



Petition for health claim to Food and Drug Administration (FDA) as specified in 21 Code of Federal Regulations 101.70(f).

Date: January 26, 2004

Name of Petitioner: Fleminger, Inc.
Attention: Sin Hang Lee, MD
Post office address: 160 Hawley Lane, Suite 205
Trumbull, CT 06611



*Received corrected pages
for pp. 144 & 149
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Subject of the petition: Food label health claim for quality natural green tea

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*** Separate attachments include**

- **Green tea EGCG Methods Development and Analytical Report** 114 pages with covering letter from Center for Advanced Food Technology, Rutgers University
- 135 publications for Section B. I.
49 publications for Section B. II.
36 publications for Section B. III.

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Food and Drug Administration
 Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)
 5100 Paint Branch Parkway
 College Park, MD 20740-3835

The undersigned, Sin Hang Lee, MD of Fleminger, Inc., submits this petition pursuant to section 403(r)(4) or 403(r)(5)(D) of the Federal Food, Drug, and Cosmetic Act with respect to quality natural green tea and its health claim.

Attached hereto, and constituting a part of this petition, are the following:

A. PRELIMINARY REQUIREMENTS:

1. Composition: The dry green tea leaf is the only substance whose infusion is to be ingested (the only component, other than water, of the green tea beverage for which the petitioner is proposing the subject health claim).

Composition of fresh green tea leaf is as follows (Graham HN. Green tea composition, consumption, and polyphenol chemistry. Prev Med 1992;21:334-350-reference grouped under B. III.), expressed in % dry weight.

Polyphenols	36.0	Carbohydrates	25.0
Methyl xanthines	3.5	Protein	15.0
Amino acids	4.0	Lignin	6.5
Organic acids	1.5	Lipids	2.0
Carotenoids	<0.1	Chlorophyll, etc.	0.5
Volatiles	<0.1	Ash	5.0

The polyphenols include 16% to 30% tea catechins in which (-)-epigallocatechin gallate (EGCG), the most abundant tea catechin, ranges from 7-13%, depending on the growing conditions and the environment of the tea plantations. The EGCG content of a green tea leaf is often used as a surrogate standard for measuring its antioxidant level.

Customarily, green tea is brewed at a 1:100 w/v dry tea leaf-to-water ratio for most tea drinkers. According to an NCI, DCPC, Chemoprevention Branch and Agent Development Committee document (NCI, DCPC, Chemoprevention Branch and Agent

Development Committee, Clinical development plan: tea extracts green tea polyphenols epigallocatechin gallate. J Cell Biochemistry 1996;26S:236-257-reference grouped under **B. II.**), a typical cup of green tea contains 710 micrograms/ml (-)-epigallocatechin gallate (EGCG) when a quality Chinese green tea was used for the brewing. For comparison, most of the green teas marketed in the Western world were found to contain only 2.0-4.2% EGCG in dry weight (Khokhar S and Magnusdottir SGM. Total phenol, catechin, and caffeine contents of teas commonly consumed in the United Kingdom. J Agric Food Chem 2002;50:565-70 - reference grouped under **B. III.**).

2. 21 CFR 101.14(b)(1): Drinking quality green tea regularly in sufficient amounts is associated with a reduction of certain forms of human cancer. The women living in a tea-producing prefecture in Japan who drink ten cups or more of green tea per day enjoy an average 8.7 more cancer-free years in their lives than those who drink less than 3 cups a day (Fujiki H, Suganuma M, Okabe S, et al. Cancer inhibition by green tea. Mutat Res. 1998 Jun 18;402(1-2):307-10 - reference grouped under **B. II.**). High green tea consumption is also associated with a lower rate of cancer recurrence in patients with early breast cancer after surgical resection of the primary tumor [Inoue M, Tajima K, Mizutani M, et al. Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. Cancer Lett 2001;167:175-82- reference grouped under **B. IJ.**

According to the 1993-1997 composite statistics, last figures available, published by the American Cancer Society, the cancer incidence rate and the mortality rate per 100,000 in the US population was 347.8 and 140.0 for women, and 475.5 and 209.7 for men, respectively. The petitioner proposes to disseminate the knowledge on how to drink green tea properly for health promotion, particularly in reducing the risk of cancers.

3. 21 CFR 101.14(b)(2). Not Applicable.
4. 21 CFR 101.14(b)(3)(i). The petitioner is advocating the use of a high quality dry tea leaf to be used for hot water infusion to prepare green tea, to be consumed in normal and consistent quantities at each meal and/or between meals.
5. 21 CFR 101.14 (b)(3)(ii). The petitioner represents that drinking green tea brewed with natural tea leaves of *Thea sinensis* is generally recognized as safe (GRAS) pursuant to Section 409 of the Federal Food, Drug and Cosmetic Act and the regulations of the Federal Food and Drug Administration promulgated thereunder, particularly 21 CFR Section 182.20.

B. SUMMARY OF SCIENTIFIC DATA:

In this submission, the petitioner demonstrates (1) that the scientific evidence in support of a category B qualified health claim outweighs the scientific evidence against such claim; (2) that the claim is appropriately qualified; and (3) that all statements in the claim are consistent with the weights of the scientific evidence.

A PubMed literature search at the website www.ncbi.nih.gov using two combinations of key search words, "Green tea and cancer risk" and "Green tea and cancer epidemiology" to search the Internet on June 12, 2003 yielded a total of 136 and 55 titles of publications, respectively. These 191 publications were accepted as the totality of publicly available scientific evidence for the analysis. Copies of these two printouts are attached herewith.

A thorough review of the publications and the references quoted by these publications found 135 scientific articles authored by investigators who have presented epidemiological data or personal observations on the subject of cancer risk related to tea consumption. Included in the 135 articles is a report by Wu et al. [Green tea and risk of breast cancer in Asian Americans. *Int J Cancer*. 2003;106(4):574-9] which was published after the date of the Internet search. This report has been included for reference because it represents the only epidemiologic study on the relationship between green tea consumption and cancer risk among residents living in the continental USA.

In addition, there are 49 articles expressing opinions on the relationship between green tea consumption and cancer risk in general, based on epidemiological data already published or based on laboratory studies. Finally, 36 recent publications on experimental or laboratory research were attached to show the current understandings of the potential mechanisms of green tea as an anticancer agent at the molecular and cellular levels.

These publications are grouped and presented as follows.

I. Epidemiological data on tea consumption and cancer risk in humans:

1. Overview tabulation analysis of 135 publications. (pages 4-7)
2. Organ-specific and overall cancer rate analyses of 135 publications. (pages 8-98)

II. General comments by medical and scientific authorities on green tea as a chemopreventive beverage in cancer risk reduction with 49 references. (pages 99-118).

III. The scientific basis of anticancer effects of green tea with 36 references (pages 119-134).

IV. The scientific evidence in support of the proposed health claim outweighs the scientific evidence against such claim (pages 135-142).

V. Answers to specific questions and summary remark (pages 143-145).

I. Epidemiological data on tea consumption and cancer risk in humans:

1. Overview tabulation analysis of publications

Of the 135 reports which have been reviewed, ninety-five (95) stated that black tea was used solely or was included in the study. For these studies, the type of tea used was black tea, or a combination of black tea and green tea, or simply "tea". Therefore, they are treated as a heterogeneous group and referred to as the "study series including black tea" since the majority of the study subjects in these reports were derived from populations in which most tea drinkers consume black tea, for example, in America and Europe. Forty (40) reports clearly stated that the study subjects were green tea drinkers. This latter group is referred to as the "green tea series".

According to the result of the study and conclusion made by the authors, each of these 135 reports was assigned to one of the following three categories:

"No relationship"= The authors of the article did not have enough evidence to demonstrate a potential benefit of tea consumption.

"Not supportive" = The investigators had focused on the potential association between tea drinking and cancer risk and found that the statistical evidence did not support the health claim of tea drinking as a means to reduce cancer risk in humans.

"supportive" = The authors of the article had statistical data or personal studies to show that tea drinking is a potential means to reduce the risk of human cancer.

In the analyses, the total number of reports classified as "No relationship" and "Not supportive" is considered to be the **negative evidence** against the current health claim submitted by the petitioner. The total number of reports classified as "supportive" is considered to be the **positive evidence** in favor of the health claim submitted by the petitioner.

In the 40 "green tea series" publications:

32 provided positive evidence in favor of the petitioner's health claim.

8 provided negative evidence which is not in favor of the petitioner's health claim.

In the 95 publications of the "study series including black tea":

79 provided negative evidence which is not in favor of drinking tea to reduce cancer risk.

16 provided positive evidence in favor of drinking tea to reduce cancer risk.

The reference numbers, the names of the authors in alphabetical order, the relevancy conclusion of the study and the type of tea used for the study in these 135 publications are presented in a list format as follows.

<u>Reference No. and AUTHORS</u>	<u>CONCLUSION</u>	<u>TYPE OF TEA</u>
1. Agudo A, Gonzalez CA, Marcos G, et al.	No relationship	Tea
2. Armstrong B, Garrod A, Doll R.	No relationship	Tea
3. Arts IC, Hollman PC, Bueno De Mesquita, et al.	No relationship	Black
4. Baron JA, Gerhardsson de Verdier M, Ekblom A.	supportive	Black
5. Bianchi GD, Cerhan JR, Parker AS, et al.	No relationship	Black
6. Blot WJ, McLaughlin JK, Chow WH.	supportive	Tea
7. Bruemmer B, White E, Vaughan TL, et al.	No relationship	Black
8. Bueno de Mesquita HB, Maisonneuve P, et al.	No relationship	Tea
9. Castelletto R, Castellsague X, Munoz N, et al.	Not supportive	Hot mate
10. Castellsague X, Munoz N, De Stefani E, et al.	supportive	Tea
11. Cheng KK, Day NE, Duffy SW, et al.	Not supportive	Hot tea
12. Chow WH, Swanson CA, Lissowska J, et al.	supportive	Black
13. Claude J, Kunze E, Frentzel-Beyme R, et al.	No relationship	Black
14. Cook-Mozaffari PJ, Azordegan F, Day NE, et al.	Not supportive	Hot tea
15. Cuzick J, Babiker AG.	No relationship	Tea
16. De Jong UW, Breslow N, Hong JG, et al.	No relationship	Tea
17. Demirer T, Icli F, Uzunalimoglu O, Kucuk O.	No relationship	Tea
18. Ellison LF.	No relationship	Black
19. Ewertz M, Gill C.	No relationship	Black
20. Fujiki H, Suganuma M, Imai K, et al.	supportive	Green
21. Fujiki H, Suganuma M, Okabe S, et al.	supportive	Green
22. Galanis DJ, Kolonel LN, Lee J, et al.	No relationship	Tea
23. Galanis DJ, Lee J, Kolonel LN.	Not supportive	Green
24. Gao YT, McLaughlin JK, Blot WJ, et al.	supportive	Green
25. Goldbohm RA, Hertog MG, Brants HA, et al.	No relationship	Black
26. Goodman MT, Morgenstern H, Wynder EL.	No relationship	Tea
27. Goto R, Masuoka H, Yoshida K, et al.	supportive	Green
28. Gupta S, Ahmad N, Mukhtar H.	supportive	Green
29. Hakim IA, Harris RB, Weisgerber UM.	supportive	Black
30. Hankin JH, Nomura A, Rhoads GG.	No relationship	Tea
31. Hansson LE, Nyren O, Bergstrom R,	supportive	Tea
32. Hara N, Sakata K, Nagai M, et al.	Not supportive	Green
33. Harnack LJ, Anderson KE, Zheng W, et al.	No relationship	Tea
34. Hartge P, Hoover R, West DW, Lyon JL.	No relationship	Tea
35. Hartman TJ, Tangrea JA, Pietinen P,	No relationship	Black
36. Heilbrun LK, Nomura A, Stemmermann GN.	No relationship	Black
37. Hiatt RA, Klatsky AL, Armstrong MA.	No relationship	Black
38. Higginson J.	No relationship	Black
39. Hoshiyama Y, Kawaguchi T, Miura.	No relationship	Green
40. Hoshiyama Y, Sasaba T.	Not supportive	Green/black
41. Howe GR, Burch JD, Miller AB, et al.	No relationship	Tea
42. Hu J, Nyren O, Wolk A, et al.	Not supportive	Hot tea
43. Huang C, Zhang X, Qiao Z, et al.	No relationship	Tea
44. Imai K, Suga K, Nakachi K.	supportive	Green
45. Inoue M, Tajima K, Hirose K, et al.	supportive	Green
46. Inoue M, Tajima K, Hirose K, et al.	Not supportive	Green
47. Inoue M, Tajima K, Mizutani M, et al.	supportive	Green
48. Iscovich J, Castelletto R, Esteve J, et al.	No relationship	Tea
49. Jain M, Howe GR, St Louis P, Miller AB.	No relationship	Tea

50. Jain MG, Hislop GT, Howe GR, et al.	supportive	Tea
51. Jensen OM, Wahrendorf J, Knudsen JB, et al.	No relationship	Tea
52. Ji BT, Chow WH, Hsing AW, et al.	supportive	Green
53. Ji BT, Chow WH, Yang G, et al.	supportive	Green
54. Kamat AM, Lamm DL.	supportive	Green
55. Kato I, Tominaga S, Matsuura A, et al.	supportive	Green
56. Kinjo Y, Cui Y, Akiba S, et al.	Not supportive	Tea/hot
57. Kinlen LJ, Willows AN, Goldblatt P, Yudkin J.	No relationship	Black
58. Klatsky AL, Armstrong MA, Friedman GD.	No relationship	Black
59. Knekt P, Jarvinen R, Seppanen R, et al.	supportive	Tea
60. Koizumi Y, Tsubono Y, Nakaya N, et al.	Not supportive	Green
61. Kono S, Ikeda M, Tokudome S, et al.	supportive	Green
62. Kono S, Shinchi K, Ikeda N, et al.	supportive	Green
63. Kono S.	supportive	Green
64. Koo LC.	No relationship	Green/black
65. Kunze E, Chang-Claude J, Frentzel-Beyme R.	No relationship	Black
66. La Vecchia C, Negri E, Decarli A, et al.	supportive	Tea
67. La Vecchia C, Negri E, Franceschi S, et al.	No relationship	Tea
68. La Vecchia C, Talamini R, Decarli A, et al.	No relationship	Tea
69. Le Marchand L, Murphy SP, Hankin JH, et al.	No relationship	Tea
70. Lee HH, Wu HY, Chuang YC, et al.	Not supportive	Green/black
71. Lu CM, Lan SJ, Lee YH, et al.	Not supportive	Tea
72. Lubin F, Ron E, Wax Y, et al.	No relationship	Black
73. Mack TM, Yu MC, Hanisch R, Henderson BE.	No relationship	Tea
74. MacMahon B, Yen S, Trichopoulos D, et al.	No relationship	Tea
75. McCredie M, Ford JM, Stewart JH.	No relationship	Tea
76. McLaughlin JK, Mandel JS, Blot WJ, et al.	Not supportive	Tea
77. Memik F, Nak SG, Gulten M, et al.	No relationship	Tea
78. Mendilaharsu M, De Stefani E, et al.	supportive	Black
79. Mettlin C.	No relationship	Tea
80. Michaud DS, Spiegelman D, Clinton SK, et al.	No relationship	Black
81. Michaud DS, Giovannucci E, Willett WC, et al.	No relationship	Tea
82. Miller AB, Howe GR, Jain M, et al.	No relationship	Tea
83. Miller CT, Neutel CI, Nair RC, et al.	No relationship	Tea
84. Mizuno S, Watanabe S, Nakamura K, et al.	Not supportive	Green/black
85. Morgan RW, Jain MG.	No relationship	Black
86. Mori M, Hariharan M, Anandakumar M,	Not supportive	Tea
87. Mu LN, Zhou XF, Ding BG, et al.	supportive	Green
88. Munoz SE, Navarro A, Lantieri MJ,	No relationship	Tea
89. Nagano J, Kono S, Preston DL, et al.	No relationship	Green
90. Nakachi K, Eguchi H, Imai K, et al.	supportive	Green
91. Nakachi K, Matsuyama S, Miyake S, et al.	supportive	Green
92. Nakachi K, Suemasu K, Suga K, et al.	supportive	Green
93. Nomura AM, Kolonel LN, Hankin JH, et al.	No relationship	Black
94. Notani PN, Jayant K.	Not supportive	Tea
95. Oguni I, Cheng SJ, Lin PZ, Hara Y.	supportive	Green
96. Ohno Y, Aoki K, Obata K, Morrison AS.	supportive	Green
97. Ohno Y, Wakai K, Genka K, et al.	supportive	Green
98. Olsen J, Kronborg O.	No relationship	Black
99. Ren A, Han X.	Not supportive	Hot tea
100. Risch HA, Burch JD, Miller AB, et al.	No relationship	Black

101.	Rosenberg L, Miller DR, Helmrich SP, et al.	No relationship	Tea
102.	Rosenblatt KA, Thomas DB, Jimenez LM, et al.	No relationship	Tea
103.	Schairer C, Brinton LA, Hoover RN.	No relationship	Tea
104.	Setiawan VW, Zhang ZF, Yu GP, et al.	supportive	Green
105.	Shibata A, Mack TM, Paganini-Hill A, et al.	supportive	Tea
106.	Shibata K, Moriyama M, Fukushima T, et al.	supportive	Green
107.	Simon D, Yen S, Cole P.	No relationship	Tea
108.	Slattery ML, West DW, Robison LM.	No relationship	Tea
109.	Slattery ML, West DW.	No relationship	Tea
110.	Stocks P.	No relationship	Tea
111.	Su LJ, Arab L.	supportive	Tea
112.	Tajima K, Tominaga S.	supportive	Green/black
113.	Tavani A, Pregnolato A, La Vecchia C, et al.	No relationship	Black
114.	Tavani A, Pregnolato A, La Vecchia C, Negri E, et al.	No relationship	Black
115.	Tewes FJ, Koo LC, Meisgen TJ, Rylander R.	Not supportive	Green/black
116.	Trichopoulos D, Ouranos G, Day NE, et al.	No relationship	Tea
117.	Tsubono Y, Nishino Y, Komatsu S, et al.	Not supportive	Green
118.	Victoria CG, Munoz N, Day NE, et al.	Not supportive	Hot mate
119.	Wakai K, Ohno Y, Obata K, Aoki K.	supportive	Green
120.	Wang M, Guo C, Li M.	supportive	Green
121.	Watanabe Y, Tada M, Kawamoto K, et al.	Not supportive	Green
122.	Whittemore AS, Paffenbarger RS Jr, Anderson K, et al.	supportive	Tea
123.	Wu AH, Yu MC, Tseng CC, et al.	supportive	Green
124.	Yang CS, Chung JY, Yang GY, et al.	supportive	Green/black
125.	Ye WM, Yi YN, Luo RX, et al.	supportive	Green
126.	Yu GP, Hsieh CC, Wang LY,	supportive	Green
127.	Yu GP, Hsieh C.	supportive	Green
128.	Yu MC, Mack TM, Hanisch R, et al	No relationship	Tea
129.	Yu Y, Hu J, Wang PP	No relationship	Tea
130.	Zatonski WA, Boyle P, Przewozniak K, et al.	supportive	Tea
131.	Zeegers MP, Dorant E, Goldbohm RA, et al.	supportive	Black
132.	Zeegers MP, Tan FE, Goldbohm RA, et al.	No relationship	Black
133.	Zhang M, Binns CW, Lee AH.	supportive	Green
134.	Zheng W, Doyle TJ, Kushi LH, et al.	No relationship	Black
135.	Zhong L, Goldberg MS, Gao YT, et al.	supportive	Green

Footnote

Tea = Report did not specify the type of tea used for the study. It usually means black tea.

Black = Report indicated that black tea was used for the study.

Green/black = Both green tea and black tea were used in the study.

Green = Only green tea was used in the study.

2. Organ-specific and overall cancer rate analyses of 135 publications

In reviewing the data of the 135 publications available in the public domain, due diligence was exercised to extract from the articles information on the potential association of tea drinking and the cancer risk in the organs in which human cancers most commonly arise. This analysis was designed to determine if tea drinking has a selective positive or negative impact on the cancer risk of a specific organ, in addition to its overall effects on cancer development. The types of cancers that have been analyzed in the literature include those of the esophagus, stomach, pancreas, colorectum, urinary bladder, prostate, kidney, lung, breast, liver, uterus and ovary. In addition to these 12 sites selected for specific analyses, eleven (11) publications are presented in the end under "Overall Cancer Rates" for the comments of the experts on tea drinking in relation to overall cancer incidence in general.

For the convenience of data reviewing, the relevant references are grouped under the subheadings of "Study series including black tea" and "Green tea series" respectively. Immediately following the subheading, the number of articles found to be in support of and the number not in support of "tea drinking associated with reduced risk of cancer in that organ" will be summarized. Then the source articles for the information are listed, all in one line, with the authors' names in alphabetical order, the reference number, the year of publication, the type of tea used for the study and the conclusion made, followed by a brief relevant statement extracted from the article.

1) Esophagus

Study Series including black tea

Eleven [11] epidemiological studies have analyzed the relationship between cancer incidence of the esophagus and tea drinking, including black tea and mate drinking. The results are summarized as follows. Several studies were primarily concerned with the thermal effects of tea on the development of esophageal cancer because drinking scalding hot liquid as a custom in certain culture is known to be associated with high incidence of esophageal cancer.

Ten [10] studies found that tea drinking is not associated with reduced risk of esophageal cancer.

One [1] study found that tea drinking is associated with reduced risk of esophageal cancer.

References

- | | | |
|---|----------|----------------|
| Castelletto R, Castellsague X, Munoz N, et al. (9) 1994 | Hot mate | Not supportive |
| Those who reported drinking mate hot or very hot as compared to those drinking it warm had an increase in risk (odds ratio, 1.7; 95% confidence interval, 1.0-2.9). | | |
| Castellsague X, Munoz N, De Stefani E, et al. (10) 2000 | Tea | supportive |
| Statistically significant protective associations were identified for high consumption of vegetables, fruits, cereals and tea. | | |

- Cheng KK, Day NE, Duffy SW, et al. (11) 1992 Hot tea Not supportive
Hot drinks are likely to increase the risk of esophageal cancer. On the other hand, the role of tea drinking, especially the use of green tea, remains to be defined better.
- Cook-Mozaffari PJ, Azordegan F, Day NE, et al. (14) 1979 Hot tea Not supportive
The use of opium, bread and tea could not be assessed in the retrospective framework.
- De Jong UW, Breslow N, Hong JG, et al. (16) 1974 Hot tea Not supportive
Esophageal cancer is more likely to occur among traditional Chinese who maintain dietary patterns which include scalding beverages.
- Hu J, Nyren O, Wolk A, et al. (42) 1994 Hot tea Not supportive
High temperature of meals and drinks was a strong risk indicator in this population. The strength of tea and overall tea consumption were independent determinants of the risk.
- La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 Tea No relationship
All the estimates for tea consumption were close to unity, the highest values being 1.4 for rectum, gallbladder, and endometrium.
- Notani PN, Jayant K. (94) 1987 Tea Not supportive
Tea drinking was observed to be a risk factor for esophageal cancers.
- Ren A, Han X. (99) 1991 Hot tea Not supportive
Hot food consumption (OR, 2.53) was a significant risk factor for esophageal cancer.
- Stocks P. (110) 1970 Tea No relationship
Tea is positively related with cancer mortality of the intestine except rectum in both sexes and with larynx, lung and breast in females. Negative associations are indicated with the stomach in both sexes and uterus and leukaemia in females.
- Victora CG, Munoz N, Day NE, et al. (118) 1987 Hot mate Not supportive
The crude odds ratio for daily mate drinkers was 1.92 relative to those drinking less frequently than daily ($p = 0.006$). Mate is a traditional beverage drunk at a very high temperature.

Green Tea Series

Six [6] epidemiological studies have analyzed the relationship between cancer incidence of the esophagus and the habit of drinking green tea. The results are summarized as follows.

Four [4] studies found that drinking green tea is associated with a reduced risk of esophageal cancer.

Two [2] studies found that drinking green tea is not associated with a reduced risk of esophageal cancer. In one of these two series, the authors stated that hot green tea may cause esophageal cancer due to its thermal effects.

References

- | | | |
|---|-----------|----------------|
| Gao YT, McLaughlin JK, Blot WJ, et al. (24) 1994 | Green | supportive |
| In this subset, statistically significant decreases in risk among tea drinkers were observed for both men (OR = 0.43; 95% CI = 0.22-0.86; P for trend = .05) and women (OR = 0.40; 95% CI = 0.20-0.77; P for trend < .001). CONCLUSIONS: This population-based, case-control study of esophageal cancer in urban Shanghai suggests a protective effect of green tea consumption. | | |
| Hara N, Sakata K, Nagai M, et al. (32) 1985 | Green | Not supportive |
| The groups of foods statistically associated with cancer death are: pork, cooking oil and shochu (low class distilled spirits) for esophageal cancer; fresh fish, salted fish, vegetables and alcoholic beverages for stomach cancer; alcoholic beverages, salted or dried fish, vegetables, bread, milk, butter, margarine, ketchup, beer and fresh fish for colonic cancer; fresh fish, salted or dried fish, salt and popular grade sake for rectal cancer; pork, popular grade sake and green tea for cancer of the biliary passages; salted or dried fish, vegetables, alcoholic beverages, oil and fresh fish for pancreatic cancer; beef, poultry, eggs and vinegar for liver cancer. Further epidemiological analyses are required to find the biological causal relationships. | | |
| Inoue M, Tajima K, Hirose K, et al. (45) 1998 | Green | supportive |
| This study comprised 1,706 histologically diagnosed cases of digestive tract cancers (185 esophagus, 893 stomach, 362 colon, 266 rectum) and a total of 21,128 non-cancer outpatients aged 40 years and over. The results suggest the potential for protective effect against site-specific digestive tract cancer by consumption of green tea and coffee, although most associations are limited only to the upper category of intake and have no clear explanation for site-specificity. | | |
| Kinjo Y, Cui Y, Akiba S, et al. (56) 1998 | Green/hot | Not supportive |
| Mortality risks of oesophageal cancer in the present cohort were substantially associated with thermal effect of hot tea, alcohol drinking and smoking. | | |
| Mu LN, Zhou XF, Ding BG, et al. (87) 2003 | Green | supportive |
| Interaction assessment showed that drinking green tea could significantly decrease the risk of gastric cancer and liver cancer among alcohol drinkers, with ORs of interaction item 0.23 (95% CI: 0.10 - 0.55) and 0.25 (95% CI: 0.11 - 0.57) respectively. CONCLUSION: Habit of drinking green tea seemed to have significant protective effects on the development of both gastric and liver cancer among alcohol drinkers while, green tea also having some protective effect on esophageal cancer among alcohol drinkers and on three kinds of cancers among cigarette smokers. | | |

Wang M, Guo C, Li M. (120) 1999 Green supportive
 Drinking green tea may decrease the ORs of esophageal and other gastric cancers (OR = 0.20 and OR = 0.28) while fruits consumption may reduce the OR of esophageal cancers (OR = 0.51).

2) Stomach

Study Series including black tea

Seventeen [17] epidemiological studies have analyzed the relationship between cancer incidence of the stomach and drinking tea, primarily black tea. The results are summarized as follows.

Fourteen [14] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the stomach.

Three [3] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the stomach.

References

Agudo A, Gonzalez CA, Marcos G, et al. (1) 1992 Tea No relationship
 No association was observed with smoking, nor with the consumption of coffee or tea.

Chow WH, Swanson CA, Lissowska J, et al. (12) 1999 Black supportive
 A significant reduction in risk was linked to daily tea drinking among women, but not among men.

Demirer T, Icli F, Uzunalimoglu O, Kucuk O. (17) 1990 Tea No relationship
 Gastric cancer patients were compared with the control group with regard to the consumption of starches, fried foods, cereals, milk, dairy products, tea, alcohol, and tobacco. No significant association was found between the consumption of a particular type of diet and cancer risk.

Galanis DJ, Kolonel LN, Lee J, et al. (22) 1998 Tea No relationship
 The daily intake of six beverages was not related with stomach cancer risk.

Goldbohm RA, Hertog MG, Brants HA et al. (25) 1996 Black No relationship
 Tea did not appear to protect against stomach and lung cancers.

Hankin JH, Nomura A, Rhoads GG. (30) 1975 Tea No relationship
 The findings suggest that the country of birth and education has lasting effects on adult eating patterns. The observed heterogeneity for specific food items and nutrients between the Nisei

and Issei-Kibei men augers well for attempts to relate such items to chronic diseases such as cancer.

- Hansson LE, Nyren O, Bergstrom R, et al. (31) 1993 Tea supportive
Cheese, fish and tea had a protective effect during adolescence.
- Heilbrun LK, Nomura A, Stemmermann GN, et al. (36) 1986 Black No relationship
Data on black tea consumption habits were recorded. Newly diagnosed cancer incidence cases have been identified: 152 colon, 151 lung, 149 prostate, 136 stomach, 76 rectum, 57 bladder, 30 pancreas, 25 liver, 12 kidney and 163 at other (miscellaneous) sites. No relationship was found.
- Higginson J. (38) 1966 Black No relationship
No significant association was found between stomach cancer risk and tea consumption
- Hoshiyama Y, Sasaba T. (40) 1992 Green/black Not supportive
The authors found no inverse association between green tea consumption and the risk of stomach cancer death.
- Kinlen LJ, Willows AN, Goldblatt P, et al. (57) 1988 Tea Not supportive
Significant relationships were found between tea consumption and deaths from stomach, lung and kidney cancers.
- La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 Tea No relationship
This integrated series of studies offers further reassuring evidence on the lack of relationship between tea and cancer risk.
- Lee HH, Wu HY, Chuang YC, et al. (70) 1990 Green/black Not supportive
A hospital-based matched case-control study carried out in Taipei metropolitan areas showed a positive association of stomach cancer with blood type A, chronic gastric diseases, cigarette smoking, alcohol drinking, green tea drinking (in 10 patients with a questionable significant *p* value between 0.05 and 0.10), as well as consumption of salted meat, cured meat, smoked food, fried food and fermented beans. This was a hospital-based case-control study consisting of 210 stomach cancer patients in Taiwan, in which green tea was used in less than 2% of hospital controls. Because Chinese patients with various illness often avoid tea drinking when certain medications are taken, particularly herbal medicines, and may be encouraged to consume more nutritious drinks (e.g., chick soup and milk), the findings from this study are difficult to interpret (see comments in Author Reply of Ref. # 23 by Bu-Tian Ji et al.). Furthermore, in Taiwan and southern China oolong teas are customarily referred to as green tea by the general public and tea merchants. Traditionally, southern Chinese and Taiwanese tend to avoid drinking green tea because of its empirically learned, notorious physiological effects in depleting body fat during famine years. This fact is reflected in Table VI of this article that the ratios of half-processed tea drinkers: green tea drinkers were 70:10 in the Case Number group and 285:14 in the Control Number group, respectively. In view of these

confounding factors, this report is not classified as a primary epidemiological study based on green tea.

- Memik F, Nak SG, Gulten M, et al. (77) 1992 Tea No relationship
No statistically significant differences in stomach cancer incidence were found with regard to the use of coffee or tea.
- Stocks P. (110) 1970 Tea supportive
Tea is positively related with cancer mortality of the intestine except rectum in both sexes and with larynx, lung and breast in females. Negative associations are indicated with the stomach in both sexes and uterus and leukaemia in females.
- Tajima K, Tominaga S. (112) 1985 Green/black No relationship
In this study, the authors found that coffee, black tea and Japanese tea showed no significant level of relative risk for cancer of the stomach, colon and rectum.
- Trichopoulos D, Ouranos G, Day NE, et al. (116) 1985 Tea No relationship
No significant associations were found with alcoholic beverages, coffee or tea.

Green tea series

Eighteen [18] epidemiological studies have analyzed the relationship between cancer incidence of the stomach and the habit of drinking green tea. The results are summarized as follows.

Thirteen [13] studies found that drinking green tea is associated with a reduced risk of stomach cancer.

Five [5] studies found that drinking green tea is not associated with a reduced risk of stomach cancer.

References

- Galanis DJ, Lee J, Kolonel LN. (23) 1997 Green Not supportive
In a Correspondence on: Cancer. 1996 Jun 15;77(12):2449-57. The authors questioned the effectiveness of green tea in chemoprevention of stomach cancer.
- Hoshiyama Y, Kawaguchi T, Miura. (39) 2002 Green No relationship
We found no inverse association between green tea consumption and the risk of stomach cancer death.
- Inoue M, Tajima K, Hirose K, et al. (46) 1994 Green Not supportive
Results obtained from this study suggest that risk factors and relative risks of gastric cancer

varied by subsite to a considerable degree. Furthermore, the joint effect of smoking and drinking may play an important role in the development of gastric cancer, especially of cardia cancer.

- Inoue M, Tajima K, Hirose K, et al. (45) 1998 Green supportive
The odds ratio (OR) of stomach cancer decreased to 0.69 (95 percent confidence interval [CI] = 0.48-1.00) with high intake of green tea (seven cups or more per day). A decreased risk was also observed for rectal cancer with three cups or more daily intake of coffee (OR = 0.46, CI = 0.26-0.81). CONCLUSIONS: The results suggest the potential for protective effect against site-specific digestive tract cancer by consumption of green tea and coffee, although most associations are limited only to the upper category of intake and have no clear explanation for site-specificity.
- Ji BT, Chow WH, Yang G, et al. (53) 1996 Green supportive
Green tea drinking was inversely associated with risk of stomach cancer arising from either subsite, with ORs of 0.77 (CI: 0.52-1.13) among female heavy drinkers, and 0.76 (CI: 0.55-1.27) among male heavy drinkers. CONCLUSIONS: Our findings provide further evidence that cigarette smoking and, possibly, alcohol consumption increase the risk of stomach carcinoma, notably of the distal segment. An inverse association with green tea drinking was also observed.
- Koizumi Y, Tsubono Y, Nakaya N, et al. (60) 2003 Green Not supportive
No association between green tea and the risk of gastric cancer: pooled analysis of two prospective studies in Japan.
- Kono S, Ikeda M, Tokudome S, et al. (61) 1988 Green supportive
A decreased risk of gastric cancer was noted among those with high consumption of green tea (10 or more cups per day).
- Kono S. (63) 2001 Green supportive
Consumption of 10 cups or more green tea per day is necessary to reduce the incidence of stomach cancer.
- Mu LN, Zhou XF, Ding BG, et al. (87) 2003 Green supportive
Green tea drinking seemed to have decreased 81%, 78%, 39% risk for the development of gastric cancer, liver cancer and esophageal cancer among alcohol drinkers. It might also have decreased 16%, 43%, 31% on the risks of developing the three kinds of cancers among cigarette smokers. Interaction assessment showed that drinking green tea could significantly decrease the risk of gastric cancer and liver cancer among alcohol drinkers, with ORs of interaction item 0.23 (95% CI: 0.10 - 0.55) and 0.25 (95% CI: 0.11 - 0.57) respectively.
- Nakachi K, Matsuyama S, Miyake S, et al. (91) 2000 Green supportive
Decreased relative risk of death from cardiovascular disease was 0.58 (0.34-0.99) for men, 0.82 (0.49-1.38) for women, and 0.72 (0.60-1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on

cumulative survival, using the life table. The relative risk for cancers of the colorectum, liver and stomach was most notably reduced.

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| Oguni I, Cheng SJ, Lin PZ, Hara Y. (95) 1992 | Green | supportive |
| In the midwest areas of Shizuoka Prefecture, where green tea is the staple product, the standardized mortality ratio (SMR) for cancer of all sites and stomach cancer was much lower than the average ratio for Japanese people of both sexes. | | |
| Setiawan VW, Zhang ZF, Yu GP, et al. (104) 2001 | Green | supportive |
| Inverse association was observed between green tea drinking and chronic gastritis and stomach cancer risks. After adjusting for age, gender, education, body mass index, pack-years of smoking and alcohol drinking, ORs of green tea drinking were 0.52 (95% CI: 0.29-0.94) and 0.49 (95% CI: 0.31-0.77) for stomach cancer and chronic gastritis, respectively. In addition, dose-response relationships were observed with years of green tea drinking in both diseases. The results provide further support on the protective effect of green tea against stomach cancer. This is the first time that green tea drinking was found to be protective against chronic gastritis, which may be of importance when designing intervention strategies for stomach cancer and its pre-malignant lesions in the high-risk population. | | |
| Shibata K, Moriyama M, Fukushima T, et al. (106) 2000 | Green | supportive |
| High green tea consumption (more than 10 cups per day) among the subjects living in a tea-farming village was negatively associated with the risk of chronic atrophic gastritis, even after adjustment for H. pylori infection and lifestyle factors associated with green tea consumption (OR = 0.63; 95% CI, 0.43-0.93). The results support the hypothesis that high green tea consumption prevents chronic atrophic gastritis, a condition known to be associated with stomach cancer development. | | |
| Tsubono Y, Nishino Y, Komatsu S, et al. (117) 2001 | Green | Not supportive |
| In a population-based, prospective cohort study in Japan, we found no association between green-tea consumption and the risk of gastric cancer. | | |
| Wang M, Guo C, Li M. (120) 1999 | Green | supportive |
| Drinking green tea may decrease the ORs of esophageal and other gastric cancers (OR = 0.20 and OR = 0.28). | | |
| Ye WM, Yi YN, Luo RX, et al. (125) 1998 | Green | supportive |
| A population-based case-control study was carried out in high-risk areas of gastric cancer in Fujian, a province known to produce teas. Among many dietary factors, green tea might have protective effects against gastric cancer. | | |
| Yu GP, Hsieh C. (127) 1991 | Green | supportive |
| Low consumption of strong tea was significantly associated with stomach cancer incidence. | | |

Yu GP, Hsieh CC, Wang LY, et al. (126) 1995

Green supportive

A total of 711 cases and 711 matched controls completed the interview. Information was obtained on the types of tea used, age when habitual tea drinking started, frequency of new batches of tea leaves used per day, number of cups brewed from each batch, total duration of drinking for each batch, strength and temperature of the tea consumed. Statistical analysis was based on modelling through conditional logistic regression. After adjusting for age, gender, place of residence, education, birthplace, alcohol consumption, and cigarette smoking, the odds ratio (OR) comparing drinkers of green tea with nondrinkers was 0.71 (95 percent confidence interval = 0.54-0.93). The adjusted OR decreased with increasing number of new batches of the green tea consumed each day (P value trend = 0.006). With the largest series of stomach cancer cases to date, this study found green-tea consumption associated with lower risk of stomach cancer. Among drinkers of green tea, the risk of stomach cancer did not depend on the age when habitual green-tea drinking started. Green tea may disrupt gastric carcinogenesis at both the intermediate and the late stages.

3) Pancreas

Study Series including black tea

Fifteen [15] epidemiological studies have analyzed the relationship between cancer incidence of the pancreas and drinking tea, primarily black tea. The results are summarized as follows.

Twelve [12] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the pancreas.

Three [3] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the pancreas.

References

Bueno de Mesquita HB, Maisonneuve P, et al. (8) 1992

Tea No relationship

Lifetime consumption of tea and of ground, instant and decaffeinated coffee was not associated with risk.

Cuzick J, Babiker AG. (15) 1989

Tea No relationship

Smoking was a clear risk factor, but cases and controls were very similar with respect to tea and coffee drinking habits.

Harnack LJ, Anderson KE, Zheng W, et al. (33) 1997

Tea No relationship

Tea intake was not related to cancer incidence.

Hiatt RA, Klatsky AL, Armstrong MA. (37) 1988

Tea No relationship

We found no evidence of increased risk associated with coffee, tea, or alcoholic beverages.

- Jain M, Howe GR, St Louis P, Miller AB. (49) 1991 Tea No relationship
Results are reported from a population-based study of 249 cases of pancreas cancer and 505 controls carried out in Toronto, Canada, between 1983 and 1986. Lifetime consumption of coffee and alcohol and medical histories was assessed by personal interviews. No evidence of any association was found with different types of coffee, tea or alcohol after adjusting for smoking, calories and fibre intake.
- La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 Tea No relationship
All the estimates for tea consumption were close to unity, including pancreatic cancer.
- Mack TM, Yu MC, Hanisch R, Henderson BE. (73) 1986 Tea No relationship
There was no link between pancreas cancer and past consumption of tea, carbonated beverages, beer, or spirits; and an association with coffee consumption was inconsistent.
- MacMahon B, Yen S, Trichopoulos D, et al. (74) 1981 Tea No relationship
There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea.
- Michaud DS, Giovannucci E, Willett WC, et al. (81) 2001 Tea No relationship
No statistically significant associations were observed for intakes of tea and cancer risk.
- Mizuno S, Watanabe S, Nakamura K, et al. (84) 1992 Green/black Not supportive
No consistent associations were found with coffee, black tea or alcohol consumption.
- Mori M, Hariharan M, Anandakumar M, et al. (86) 1999 Tea Not supportive
Heavy cigarette smoking and drinking large amounts of coffee and/or tea everyday were positively related to the risk of pancreatic duct adenocarcinoma alone
- Shibata A, Mack TM, Paganini-Hill A, et al (105) 1994 Tea supportive
Risk of pancreatic cancer decreased with increasing tea consumption but was unrelated to coffee consumption.
- Whittemore AS, Paffenbarger RS Jr, Anderson K, et al. (122) 1983 Tea supportive
The relative risk for coffee drinking adjusted for smoking was 1.1 (0.7-1.8). In contrast, collegiate tea consumption was associated with a reduction in pancreatic cancer risk.
- Zatonski WA, Boyle P, Przewozniak K, et al. (130) 1993 Tea supportive
There was a strongly significant trend of decreasing risk with increasing lifetime consumption of tea ($p < 0.001$), which was also apparent when the analysis was restricted to subjects who were interviewed directly.
- Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 Black No relationship
No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary. This study suggests that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women.

Green tea series

Two [2] studies found that drinking green tea is associated with a reduced risk of pancreatic cancer.

References

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| Goto R, Masuoka H, Yoshida K, et al. (27) 1990 | Green | supportive |
| Significantly decreased risks were associated with consumption of raw vegetables and green tea. The risk increased significantly with consumption of the fat of meat, boiled fish, coffee, black tea and alcoholic beverages. | | |
| Ji BT, Chow WH, Hsing AW, et al. (52) 1997 | Green | supportive |
| An inverse association with each cancer was observed with increasing amount of green tea consumption, with the strongest trends for rectal and pancreatic cancers. | | |

4) Colorectum

Study Series including black tea

Thirteen [13] epidemiological studies have analyzed the relationship between cancer incidence of the colorectum and drinking tea, primarily black tea. The results are summarized as follows.

Ten [10] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the colorectum.

Three [3] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the colorectum.

References

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| Baron JA, Gerhardsson de Verdier M, et al. (4) 1994 | Black | supportive |
| For tea, there was no association with colon cancer risk, but the odds ratio for rectal cancer was 0.56 (95% confidence interval, 0.34-0.90) for those drinking 2 or more cups per day compared with those drinking none. | | |
| Hartman TJ, Tangrea JA, Pietinen P, et al. (35) 1998 | Black | No relationship |
| This study does not support the hypothesis that coffee and tea protect against colorectal cancer risk. | | |

- Heilbrun LK, Nomura A, Stemmermann GN, et al. (36) 1986 Black No relationship
Compared to almost-never drinkers, men habitually drinking black tea more than once/day had an increased relative risk (RR) for rectal cancer (RR = 4.2).
- Kinlen LJ, Willows AN, Goldblatt P, Yudkin J. (57) 1988 Black No relationship No
evidence of a dose-response relationship was found for rectal, colon or prostate cancer.
- La Vecchia C, Negri E, Franceschi S, et al. (67) Tea Not supportive
All the estimates for tea consumption were close to unity, the highest values being 1.4 for rectum, gallbladder, and endometrium.
- Miller AB, Howe GR, Jain M, et al. (82) 1983 Tea No relationship
The study included 348 patients with colon cancer, 194 with rectal cancer, 542 neighbourhood controls individually matched to the cases on the basis of age and sex and a second control series of 535 surgical hospital controls frequency matched to the cases. Tea was not found to be related to cancer risk of the colon and rectum.
- Munoz SE, Navarro A, Lantieri MJ, et al. (88) 1998 Tea No relationship
The consumption of coffee, mate and tea was not significantly related to colorectal cancer.
- Olsen J, Kronborg O. (98) 1993 Black No relationship
Coffee consumption showed a clear protective effect. Consumers of 4-7 cups per day had an OR of 0.5 (95% CI: 0.3-0.8) and heavy consumers of ≥ 8 cups had an OR of 0.3 (95% CI: 0.1-0.6). Neither tea nor alcohol consumption was related to adenoma risks.
- Stocks P. (110) 1970 Tea Not supportive
Tea is positively related with cancer mortality of the intestine except rectum in both sexes.
- Su LJ, Arab L. (111) 2002 Tea supportive
After adjusting for confounders, the relative risks of colon cancer are 0.57 (95% confidence interval (CI) 0.42, 0.78) and 0.59 (95% 1.00) for subjects who consumed ≤ 1.5 cups and > 1.5 cups per day, respectively, compared with non-tea users..
- Tajima K, Tominaga S. (112) 1985 Green/black No relationship
In this study, the authors found that coffee, black tea and Japanese tea showed no significant level of relative risk for cancer of the stomach, colon and rectum.
- Tavani A, Pregnotato A, La Vecchia C, et al. (114) 1997 Black No relationship
Tea consumption was generally limited to 1 cup/day or to occasional intake and did not substantially modify the risk of colon and rectal cancers.
- Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 Black supportive
Inverse associations with increasing frequency of tea drinking were seen for cancers of the digestive tract (p for trend, 0.04) and the urinary tract (p for trend, 0.02). For women who

reported drinking ≥ 2 cups (474 ml) of tea per day, compared with those who never or occasionally drank tea, the relative risk for digestive tract cancers was 0.68 (95% confidence interval (CI) 0.47-0.98) and for urinary tract cancers, 0.40 (95% CI 0.16-0.98).

Green tea series

Seven [7] epidemiological studies have analyzed the relationship between cancer incidence of the colorectum and the habit of drinking green tea. The results are summarized as follows.

Six [6] studies found that drinking green tea is associated with a reduced risk of colorectal cancer.

One [1] study found that drinking green tea is not associated with a reduced risk of colorectal cancer.

References

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| Inoue M, Tajima K, Hirose K, et al. (45) 1998 | Green | supportive |
| This study comprised 1,706 histologically diagnosed cases of digestive tract cancers (185 esophagus, 893 stomach, 362 colon, 266 rectum) and a total of 21,128 non-cancer outpatients aged 40 years and over. The results suggest the potential for protective effect against site-specific digestive tract cancer by consumption of green tea and coffee, although most associations are limited only to the upper category of intake and have no clear explanation for site-specificity. | | |
| Ji BT, Chow WH, Hsing AW, et al. (52) 1997 | Green | supportive |
| An inverse association with each cancer was observed with increasing amount of green tea consumption, with the strongest trends for rectal and pancreatic cancers. | | |
| Kato I, Tominaga S, Matsuura A, et al. (55) 1990 | Green | supportive |
| Daily intake of hot green tea was inversely associated with the risks of distal colon and rectal adenomas and colon cancer. | | |
| Kono S, Shintani K, Ikeda N, et al. (62) 1991 | Green | supportive |
| Among a limited range of foods and beverages, the consumption of rice, green tea and instant coffee tended to be associated with a decreased risk of adenomatous polyps. | | |
| Nakachi K, Matsuyama S, Miyake S, et al. (91) 2000 | Green | supportive |
| Decreased relative risk of death from cardiovascular disease was 0.58 (0.34-0.99) for men, 0.82 (0.49-1.38) for women, and 0.72 (0.60-1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on cumulative survival, using the life table. The relative risk for cancers of the colorectum, liver and stomach was most notably reduced. | | |

Oguni I, Cheng SJ, Lin PZ, Hara Y. (95) 1992 Green supportive
In the midwest areas of Shizuoka Prefecture, where green tea is the staple product, the standardized mortality ratio (SMR) for cancer of all sites and stomach cancer was much lower than the average ratio for Japanese people of both sexes.

Watanabe Y, Tada M, Kawamoto K, et al. (121) 1984 Green Not supportive
Green tea might be linked to risk of colorectal cancer although the data did not allow the authors to reach a significant interpretation.

5) Urinary Bladder

Study Series including black tea

Twenty-five [25] epidemiological studies have analyzed the relationship between cancer incidence of the bladder and drinking tea, primarily black tea. The results are summarized as follows.

Twenty-two [22] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the urinary bladder.

Three [3] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the urinary bladder.

References

Bianchi GD, Cerhan JR, Parker AS, et al. (5) 2000 Black No relationship
This study offers only minimal support for an inverse association between tea consumption and bladder or kidney cancer risk.

Bruemmer B, White E, Vaughan TL, et al. (7) 1997 Black No relationship
No association was found between the incidence of bladder cancer and the intake of water, coffee, tea, diet soft drinks, alcohol, or liquids from tap for men or women.

Claude J, Kunze E, Frentzel-Beyme R, et al. (13) 1986 Black No relationship
Controlling for smoking, an elevated risk of 2.3 for drinking more than four cups of coffee per day and significant odds ratios of 2.1 and 2.8 for a daily consumption of 0.5-1.0 liter and above 1.0 liter of beer, respectively, were noted among men. Tea was not significantly related to risk.

Hartge P, Hoover R, West DW, Lyon JL. (34) 1983 Tea No relationship
There were no significant associations between black tea consumption and cancer of bladder.

Heilbrun LK, Nomura A, Stemmermann GN. (36) 1986 Black No relationship
There were no significant associations between black tea consumption and cancer of bladder.

- Howe GR, Burch JD, Miller AB, et al. (41) 1980 Tea No relationship
No risk was observed in males or females consuming nitrate-containing foods, beverages other than coffee, or fiddlehead greens.
- Iscovich J, Castelletto R, Esteve J, et al. (48) 1987 Tea No relationship
No association was found with the use of saccharin and tea drinking.
- Jensen OM, Wahrendorf J, Knudsen JB, et al. (51) 1986 Tea No relationship
This population-based case-control study provides no evidence of an isolated influence of coffee drinking, tea drinking or caffeine intake on bladder cancer risk.
- Kinlen LJ, Willows AN, Goldblatt P, et al. (57) 1988 Black No relationship
No relationship was recognized between tea drinking and bladder cancer risk.
- Kunze E, Chang-Claude J, Frentzel-Beyme R. (65) 1992 Black No relationship
No relationship between tea drinking and bladder cancer risk.
- La Vecchia C, Negri E, Decarli A, et al. (66) 1989 Tea supportive
The risk of bladder cancer was not related to scores of fat and measures of alcohol consumption; the risk was elevated in coffee drinkers (although there was no tendency to rise with higher consumption), but it was reduced in tea drinkers.
- La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 Tea No relationship
All the estimates for tea consumption were close to unity.
- Lu CM, Lan SJ, Lee YH, et al. (71) 1999 Tea Not supportive
Our results suggest that tea consumption is associated with an increased risk of bladder cancer.
- Michaud DS, Spiegelman D, Clinton SK, et al. (80) 1999 Black No relationship
CONCLUSIONS: A high fluid intake (not necessarily tea) is associated with a decreased risk of bladder cancer in men. .
- Miller CT, Neutel CI, Nair RC, et al. (83) 1978 Tea No relationship
Tea consumption was not found to be related to bladder cancer risk.
- Morgan RW, Jain MG. (85) 1974 Tea No relationship
Tea and coffee intake did not increase the relative risk of bladder cancer.
- Nomura AM, Kolonel LN, Hankin JH, et al. (93) 1991 Black No relationship
There were no statistically significant or consistent differences between cases and controls in the intake of artificial sweeteners and tea.
- Risch HA, Burch JD, Miller AB, et al. (100) 1988 Black No relationship
Subjects were interviewed concerning their histories of exposure to a number of dietary

factors, including table-top artificial sweeteners, low calorie foods and drinks, beverages containing caffeine or ethanol, and certain other food items. Tea was not related to bladder cancer risk.

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| Simon D, Yen S, Cole P. (107) 1975 | Tea | No relationship |
| Data on coffee drinking, tea drinking, use of coffee additives showed no relationship to bladder cancer risk. | | |
| Slattery ML, West DW, Robison LM. (108) 1988 | Tea | No relationship |
| Tea consumption in non-cigarette smokers increased bladder cancer risk (OR = 2.25). | | |
| Stocks P. (110) 1970 | Tea | No relationship |
| Teawas not found to be related with bladder cancer mortality. | | |
| Yu Y, Hu J, Wang PP, et al. (129) 1997 | Tea | No relationship |
| There was no association between the consumption of alcohol or tea, or types of water supply, with bladder cancer risk. | | |
| Zeegers MP, Tan FE, Goldbohm RA, et al. (132) 2001 | Black | No relationship |
| The consumption of tea seems not to be related to an increased risk of urinary tract cancer. | | |
| Zeegers MP, Dorant E, Goldbohm RA, et al. (131) 2001 | Black | supportive |
| Tea consumption was inversely associated with bladder cancer. | | |
| Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 | Black | supportive |
| Inverse associations with increasing frequency of tea drinking were seen for cancers of the digestive tract (p for trend, 0.04) and the urinary tract (p for trend, 0.02). For women who reported drinking > or = 2 cups (474 ml) of tea per day, compared with those who never or occasionally drank tea, the relative risk for digestive tract cancers was 0.68 (95% confidence interval (CI) 0.47-0.98) and for urinary tract cancers, 0.40 (95% CI 0.16-0.98). | | |

Green tea series

Four [4] epidemiological studies have analyzed the relationship between cancer incidence of the urinary bladder and the habit of drinking green tea. The results are summarized as follows.

Three [3] studies found that drinking green tea is associated with a reduced risk of bladder cancer.

One [1] study found that drinking green tea is not associated with a reduced risk of bladder cancer.

References

- Kamat AM, Lamm DL. (54) 2002 Green supportive
 Among the numerous other compounds and dietary substances purported to have chemopreventive effect, soybeans, garlic, and green tea stand out as having the greatest promise and can freely be recommended to patients. There is a mistaken notion that simply because an agent is naturally occurring, it cannot be as beneficial as taking a substance synthesized in the laboratory. Encouraging patients to follow an essentially healthy food habit lifestyle will be a significant contribution in the fight against cancer.
- Nagano J, Kono S, Preston DL, et al. (89) 2001 Green No relationship
 Conclusion: Our findings do not provide evidence that regular green tea consumption is related to reduced cancer risks, including bladder cancer. This failure may be due to some crudeness in the assessment of green tea intake; green tea consumption was determined only in terms of self-reported daily frequency of drinking, and the highest category was five or more cups per day. **Bioactivity of a cup of green tea obviously differs** by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the pot. **In Shizuoka prefecture, which has the highest production of green tea leaves in Japan, residents of towns with low mortality from stomach cancer were found not only to drink green tea more frequently, but also to renew tea leaves more frequently than those of a town with high mortality from stomach cancer.**
- Ohno Y, Aoki K, Obata K, Morrison AS. (96) 1985 Green supportive
 Reduced risk of significance was suggested for the intake of black tea and matcha (powdered green tea) in females and of fruit juice in males.
- Wakai K, Ohno Y, Obata K, Aoki K. (119)1993 Green supportive
 Univariate analyses revealed significant associations of 5-year survivorship with educational attainment, marital status, drinking habits and consumption of green tea in males, and age at first consultation, histological type and grade of tumor, stage and distant metastasis in both sexes.

6) Prostate

Study Series including black tea

Four [4] epidemiological studies have analyzed the relationship between cancer incidence of the prostate and drinking tea, primarily black tea. The results are summarized as follows.

Two [2] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the prostate.

Two [2] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the prostate.

7) Kidney

Study Series including black tea

Eight [8] epidemiological studies have analyzed the relationship between cancer incidence of the kidney and drinking tea, primarily black tea. All 8 studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the kidney.

References

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| Armstrong B, Garrod A, Doll R. (2) 1976 | Tea | No relationship |
| Interviews were obtained with 106 patients with adenocarcinoma of the renal parenchyma, 33 patients with carcinoma of the renal pelvis and 139 individually matched control patients. Tea and coffee consumption was not related to cancer risk. | | |
| Goodman MT, Morgenstern H, Wynder EL. (26) 1986 | Tea | No relationship |
| Beverages such as caffeinated coffee, soft drinks, and tea, in addition to physical activity and occupation, were unrelated to the occurrence of disease. | | |
| Kinlen LJ, Willows AN, Goldblatt P, et al. (57) 1988 | Tea | Not supportive |
| Significant relationships were found between tea consumption and deaths from stomach, lung and kidney cancers. | | |
| La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 | Tea | No relationship |
| All the estimates for tea consumption were close to unity. | | |
| McCredie M, Ford JM, Stewart JH. (75) 1988 | Tea | No relationship |
| No association was found with consumption of aspirin, paracetamol, prescribed medicines, tea, coffee or animal proteins other than milk, or with the type of fat or oil used for cooking or spreading. | | |
| McLaughlin JK, Mandel JS, Blot WJ, et al. (76) 1984 | Tea | Not supportive |
| Positive associations were observed for long-term use of phenacetin-containing analgesics, heavy meat consumption, and heavy tea drinking (females only). | | |
| Stocks P. (100) 1970 | Tea | No relationship |
| Tea was not found to be related with renal cell carcinoma mortality. | | |
| Yu MC, Mack TM, Hanisch R, et al (128) 1986 | Tea | No relationship |
| Tea consumption was not found to be related to risk of renal cell carcinoma. | | |

Green tea series

None available.

8) Lung

Study Series including black tea

Eleven [11] epidemiological studies have analyzed the relationship between cancer incidence of the lung and drinking tea, primarily black tea. The results are summarized as follows.

Nine [9] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the lung.

Two [2] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer of the lung.

References

- Arts IC, Hollman PC, Bueno De Mesquita HB, et al. (3) 2001 Black No relationship
After multivariate adjustment, catechin intake was not associated with epithelial cancer (risk ratio [RR] from lowest to highest tertile: 1.00, 0.75, 0.94; p for trend: 0.82), or lung cancer (RR from lowest to highest tertile: 1.00, 0.72, 0.92; p for trend: 0.80).
- Heilbrun LK, Nomura A, Stemmermann GN, et al. (36) 1986 Black No relationship
Data on black tea consumption habits were recorded. Newly diagnosed cancer incidence cases have been identified: 152 colon, 151 lung, 149 prostate, 136 stomach, 76 rectum, 57 bladder, 30 pancreas, 25 liver, 12 kidney and 163 at other (miscellaneous) sites. No relationship was found.
- Huang C, Zhang X, Qiao Z, et al. (43) 1992 Tea No relationship
Association of tea, alcohol, garlic or mushroom, respectively, with the risk was also not observed.
- Knekt P, Jarvinen R, Seppanen R, et al. (59) 1997 Tea supportive
The association between flavonoid intake and lung cancer incidence was not due to the intake of antioxidant vitamins or other potential confounding factors.
- Koo LC. (64) 1988 Green/black No relationship
The protective effects of diet, i.e., higher consumption of leafy green vegetables, carrots, tofu, fresh fruit, and fresh fish, were confined mostly to those with adenocarcinoma or large cell tumors. Only fresh fruit was found to positively, and smoked meats to negatively, affect the risk of squamous or small cell tumors. Foods high in vitamin C, retinol, and calcium seemed to exert larger effects.
- Le Marchand L, Murphy SP, Hankin JH, et al. (69) 2000 Tea No relationship
After adjusting for smoking and intakes of saturated fat and beta-carotene, we found statistically significant inverse associations between lung cancer risk and the main food sources of the flavonoids quercetin (onions and apples) and naringin (white grapefruit). No association was found for important food sources of other flavonoids, such as those of tea.

Mendilaharsu M, De Stefani E, Deneo-Pellegrini H, et al. (78) 1998 Black supportive
Whereas coffee drinking had no effect on the lung cancer risk of the cigarette-smoking men in this study, black tea consumption decreased this risk. Heavy drinkers of tea (two or more cups of tea per day) were associated with a reduced risk of 0.34 (95% CI 0.14-0.84).

Mettlin C. (79) 1989 Tea No relationship
Frequency of consumption of milk, coffee, tea, soft drinks and alcoholic beverages was studied. Significant risk variations were observed, but dose-response patterns were not evident.

Stocks P. (110) 1970 Tea Not supportive
Tea is positively related with cancer mortality of the intestine except rectum in both sexes and with larynx, lung and breast in females. Negative associations are indicated with the stomach in both sexes and uterus and leukaemia in females.

Tewes FJ, Koo LC, Meisgen TJ, Rylander R. (115) 1990 Green/black Not supportive
Analysis of the data demonstrated an adjusted and statistically significant increased lung cancer risk of 2.7 among those (23 patients) who drank green tea. However, no statistical difference was achieved if cigarette smoking was taken into account (Koo, 1988).

Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 Black No relationship
No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary. This study suggests that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women.

Green tea series

Two [2] epidemiological studies have analyzed the relationship between cancer incidence of the lung and the habit of drinking green tea. Both found that drinking green tea is associated with a reduced risk of lung cancer.

References

Ohno Y, Wakai K, Genka K, et al. (97) 1995 Green supportive
Daily tea consumption significantly decreased the risk of squamous cell carcinoma in males and females, the odds ratios being 0.50 (95% confidence interval 0.27-0.93) and 0.08 (0.01-0.68), respectively. These findings suggest a protective effect of tea consumption against lung cancer in humans.

Zhong L, Goldberg MS, Gao YT, et al. (135) 2001 Green supportive
Among nonsmoking women, consumption of green tea was associated with a reduced risk of lung cancer (OR = 0.65; 95% CI = 0.45-0.93), and the risks decreased with increasing

consumption. We found little association, however, among women who smoked (OR = 0.94; 95% CI = 0.40-2.22). The inconsistency in the association between drinking tea and the risk of lung cancer reported in previous studies may in part be due to inadequate control of confounding of active smoking.

9) Breast

Study Series including black tea

Eight [8] epidemiological studies have analyzed the relationship between cancer incidence of the breast and drinking tea, primarily black tea. All 8 studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the breast.

References

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|---|-------|-----------------|
| Ewertz M, Gill C. (19) 1990 | Black | No relationship |
| The risk of breast cancer was not associated with consumption of vegetables rich in beta-carotene, multi-vitamin tablets or other dietary supplements, coffee, tea, sugar or artificial sweeteners. | | |
| La Vecchia C, Talamini R, Decarli A, et al. (68) 1986 | Tea | No relationship |
| The relationship of breast cancer to coffee drinking habits was evaluated in a case-control study of 616 women with breast cancer and 616 control subjects with nonmalignant disorders, apparently unrelated to coffee consumption. Compared with women who had never drunk coffee, the relative risk estimates for those women who drank less than two, two or three, and four or more cups each day were 1.5, 1.3, and 1.0, respectively. There was no apparent association with duration of consumption or use of other methylxanthine-containing beverages. | | |
| Lubin F, Ron E, Wax Y, Modan B. (72) 1985 | Black | No relationship |
| When comparison was done to both matched control groups, a nonsignificant negative association was found between consumption of cups of coffee and breast cancer (odds ratios of greater than or equal to 4 cups of coffee/day vs. less than or equal to 1 per week = 0.6 for BC/NC and 0.7 for BC/SC). The association with tea consumption was insignificant. | | |
| Rosenberg L, Miller DR, Helmrigh SP, et al. (101) 1985 | Tea | No relationship |
| Coffee consumption was not associated with an increase in the risk of breast cancer among women with a history of fibrocystic breast disease, nor were tea or decaffeinated coffee associated with an increase in the risk of breast cancer. | | |
| Rosenblatt KA, Thomas DB, Jimenez LM, et al. (102) 1999 | Tea | No relationship |
| The study was concerned with dietary factors in developing breast cancer in men.
CONCLUSIONS: The observed associations are not consistent with findings from studies of breast cancer in women and probably do not represent causal relationships. Dietary factors are unlikely to be strong determinants of breast cancer in men. | | |

- Schairer C, Brinton LA, Hoover RN. (103) 1987 Tea No relationship
There was no evidence of a positive association between methylxanthine consumption and risk of breast cancer. In fact, there was some suggestion of a negative association, particularly in women diagnosed after age 50. In addition, there was no evidence of increased risk with past or recent methylxanthine consumption, or with the consumption of caffeine or specific beverages, most notably brewed or instant caffeinated coffee and tea.
- Tavani A, Pregnolato A, La Vecchia C, et al. (113) 1998 Black No relationship
Tea consumption was also low and not associated with the risk of breast cancer (OR 0.94, 95% CI 0.85-1.03).
- Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 Black No relationship
No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary.

Green tea series

Four [4] epidemiological studies have analyzed the relationship between cancer incidence of the breast and the habit of drinking green tea. All 4 studies found that drinking green tea is associated with a reduced risk of breast cancer.

References

- Inoue M, Tajima K, Mizutani M, et al. (47) 2001 Green supportive
A decreased risk (HR: hazard ratio) for recurrence of breast cancer adjusted for stage was observed with consumption of three or more daily cups of green tea (HR=0.69, 95% confidence interval (95%CI)=0.47-1.00). Particularly in stage I, the HR was decreased statistically significantly (HR=0.43, 95%CI=0.22-0.84). A similar tendency was observed for stage II subjects, but was not present among more advanced stages. Although careful interpretation is needed, these results suggest the possibility that regular green tea consumption may be preventive against recurrence of breast cancer in early stage cases.
- Nakachi K, Suemasu K, Suga K, et al. (92) 1998 Green supportive
We found that increased consumption of green tea was correlated with decreased recurrence of stage I and II breast cancer ($P < 0.05$ for crude disease-free survival); the recurrence rate was 16.7 or 24.3% among those consuming ≥ 5 cups or ≤ 4 cups per day, respectively, in a seven-year follow-up of stage I and II breast cancer, and the relative risk of recurrence was 0.564 (95% confidence interval, 0.350-0.911) after adjustment for other lifestyle factors. However, no improvement in prognosis was observed in stage III breast cancer. Our results indicate that increased consumption of green tea prior to clinical cancer onset is significantly associated with improved prognosis of stage I and II breast cancer, and this association may be related to a modifying effect of green tea on the clinical characteristics of the cancer.

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|---|-------|------------|
| Oguni I, Cheng SJ, Lin PZ, Hara Y. (95) 1992 | Green | supportive |
| In the midwest areas of Shizuoka Prefecture, where green tea is the staple product, the standardized mortality ratio (SMR) for cancer of all sites and stomach cancer was much lower than the average ratio for Japanese people of both sexes. | | |
| Wu AH, Yu MC, Tseng CC, et al. (123) 2003 | Green | supportive |
| Risk of breast cancer was not related to black tea consumption. In contrast, green tea drinkers showed a significantly reduced risk of breast cancer, and this was maintained after adjusting for age, specific Asian ethnicity, birthplace, age at menarche, parity, menopausal status, use of menopausal hormones, body size and intake of total calories and black tea. Compared to women who did not drink green tea regularly (i.e., less than once a month), there was a significant trend of decreasing risk with increasing amount of green tea intake, adjusted odds ratios being 1.00, 0.71 (95% confidence interval [CI] 0.51-0.99) and 0.53 (95% CI 0.35-0.78), respectively, in association with no, 0-85.7 and >85.7 ml of green tea per day. The significant inverse association between risk of breast cancer and green tea intake remained after further adjustment for other potential confounders, including smoking; alcohol, coffee and black tea intake; family history of breast cancer; physical activity; and intake of soy and dark green vegetables. While both green tea and soy intake had significant, independent protective effects on breast cancer risk, the benefit of green tea was primarily observed among subjects who were low soy consumers. Similarly, the protective effect of soy was primarily observed among subjects who were nondrinkers of green tea. In summary, our results point to an important role of both green tea and soy intake in relation to breast cancer risk in Asian-American women. | | |

10) Liver

Study Series including black tea

Three [3] epidemiological studies have analyzed the relationship between cancer incidence of the liver and drinking tea, primarily black tea. All 3 studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the liver.

References

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|--|-------|-----------------|
| Heilbrun LK, Nomura A, Stemmermann GN. (36) 1986 | Black | Not supportive |
| There was no significant association between black tea consumption and liver cancer. | | |
| La Vecchia C, Negri E, Franceschi S, et al. (67) 1992 | Tea | Not supportive |
| All the estimates for tea consumption were close to unity, including liver cancer. | | |
| Stocks P. (110) 1970 | Tea | No relationship |
| Tea was not found to be related with liver cancer mortality. | | |

References

Stocks P. (110) 1970

Tea is positively related with cancer mortality of the intestine except rectum in both sexes and with larynx, lung and breast in females. Negative associations are indicated with the stomach in both sexes and uterus and leukaemia in females.

Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996	Black	No relationship
No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary. This study suggests that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women.		

Green tea series

One epidemiological study has analyzed the relationship between cancer incidence of the uterus and the habit of drinking green tea and found that drinking green tea is associated with a reduced risk of uterine cancer.

Reference

Oguni I, Cheng SJ, Lin PZ, Hara Y. (95) 1992 Green supportive
In the midwest areas of Shizuoka Prefecture, where green tea is the staple product, the
standardized mortality ratio (SMR) for cancer of all sites and stomach cancer was much
lower than the average ratio for Japanese people of both sexes.

12) Ovary

Study Series including black tea

One epidemiological study analyzed the relationship between cancer incidence of the ovary and drinking tea, primarily black tea and found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer of the ovary.

Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996	Black	No relationship
No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary. This study suggests that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women.		

Green tea series

One epidemiological study has analyzed the relationship between cancer incidence of the ovary and the habit of drinking green tea and found that drinking green tea is associated with a reduced risk of ovarian cancer.

Reference

Zhang M, Binns CW, Lee AH. (133) 2002

Green supportive

The ovarian cancer risk declined with increasing frequency and duration of overall tea consumption. The adjusted odds ratio was 0.39 for those drinking tea daily and 0.23 for those drinking tea for >30 years, compared with nontea drinkers. The dose response relationships were significant, and the inverse association with ovarian cancer was observed for green tea consumption. The authors concluded that increasing frequency and duration of green tea drinking can reduce the risk of ovarian cancer.

13) Overall Cancer Rates

Study Series including black tea

Six [6] epidemiological studies have analyzed the relationship between overall cancer rates and drinking tea, primarily black tea. The results are summarized as follows.

Three [3] studies found that drinking tea, primarily black tea, is not associated with a reduced risk of cancer rates.

Three [3] studies found that drinking tea, primarily black tea, is associated with a reduced risk of cancer rates.

References

Blot WJ, McLaughlin JK, Chow WH. (6) 1997

Tea supportive

Herein epidemiologic studies around the world are reviewed to assess the rates and risks of cancer among black tea drinkers. Ecologic data suggest at most a modest benefit on total cancer, as there is considerable international variation in black tea consumption but generally small differences in overall cancer rates.

Goldbohm RA, Hertog MG, Brants HA, et al. (25) 1996

Black No relationship

This investigation does not support the hypothesis that consumption of black tea protects against four of the major cancers in humans; a cancer-enhancing effect was not evident, either.

Hakim IA, Harris RB, Weisgerber UM. (29) 2000

Black supportive

This is one of the first studies to explore the relation between different types of tea consumption and occurrence of human cancers. Our results show that tea concentration

(strength), brewing time, and beverage temperature have major influences on the potential protective effects of hot black tea in relation to skin SCC. Further studies with increased sample sizes are needed to evaluate the interrelationships between preparation techniques, tea type, and other life-style factors.

- Klatsky AL, Armstrong MA, Friedman GD. (58) 1993 Black No relationship
Except for conflicting evidence about coffee and risk of coronary disease, coffee and tea are not linked to major causes of death.
- Yang CS, Chung JY, Yang GY, et al. (124) 2000 Green/black supportive
More mechanistic and human studies in these areas will help us to understand the possible inhibitory action of tea against carcinogenesis in humans.
- Zheng W, Doyle TJ, Kushi LH, et al. (134) 1996 Black No relationship
After controlling for confounding factors, the authors found that regular tea consumption was related to a slight, but not statistically significant, reduced incidence of all cancers combined. Inverse associations with increasing frequency of tea drinking were seen for cancers of the digestive tract (p for trend, 0.04) and the urinary tract (p for trend, 0.02). For women who reported drinking ≥ 2 cups (474 ml) of tea per day, compared with those who never or occasionally drank tea, the relative risk for digestive tract cancers was 0.68 (95% confidence interval (CI) 0.47-0.98) and for urinary tract cancers, 0.40 (95% CI 0.16-0.98). Similar inverse associations were seen for specific digestive and urinary tract cancers, although site-specific analyses were not statistically significant. No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary.

Green tea series

Five [5] epidemiological studies have analyzed the relationship between overall cancer rates and the habit of drinking green tea. The results are summarized as follows.

Four [4] studies found that drinking green tea is associated with reduced cancer rates.

One [1] study found that drinking green tea is not associated with reduced cancer rates. The authors commented that bioactivity of a cup of green tea may play an important role in determining the effectiveness of drinking green tea as a chemopreventive agent.

References

- Fujiki H, Suganuma M, Imai K, Nakachi K. (20) 2002 Green supportive
Green tea and (-)-epigallocatechin gallate (EGCG) are now acknowledged cancer preventives in Japan and has made it possible for us to establish the concept of a cancer preventive beverage. For the general population, we recommend 10 cups of green tea daily supplemented with green tea tablets. For cancer patients following treatment, we here present new evidence that green tea and a cancer preventive drug, sulindac, have synergistic

preventive effects. An approach to develop green tea capsules as a cancer preventive drug in the US is discussed, aiming at taking full advantage of this cancer preventive beverage.

- Fujiki H, Suganuma M, Okabe S, et al. (21) 2001 Green supportive
The results of a 10 year prospective cohort study demonstrating the effectiveness of daily consumption of green tea in preventing cancer, and a prototype study for developing green tea beverage as cancer preventive.
- Imai K, Suga K, Nakachi K. (44) 1997 Green supportive
We found a negative association between green tea consumption and cancer incidence, especially among females drinking more than 10 cups a day. The slowdown in increase of cancer incidence with age observed among females who consumed more than 10 cups a day is consistent with the finding that increased consumption of green tea is associated with later onset of cancer. Age-standardized average annual incidence rate was significantly lower among females who consumed large amounts of green tea. Relative risk (RR) of cancer incidence was also lower among both females (RR = 0.57, 95% CI = 0.33-0.98) and males (RR = 0.68, 95% CI = 0.39-1.21) in groups with the highest consumption, although the preventive effects did not achieve statistical significance among males, even when stratified by smoking and adjusted for alcohol and dietary variables. CONCLUSION: Our epidemiological study showed that green tea has a potentially preventive effect against cancer among humans.
- Nakachi K, Eguchi H, Imai K. (90) 2003 Green supportive
The authors found an apparent delay of cancer onset/death and all cause deaths associated with increased consumption of green tea, specifically in ages before 79 in a prospective cohort study of a Japanese population with 13-year follow-up data. This is consistent with analyses of age-specific cancer death rate and cumulative survival, indicating a significant slowing of the increase in cancer death and all cause death with aging. These results indicate that daily consumption of green tea in sufficient amounts will help to prolong life by avoiding pre-mature death, particularly death caused by cancer.
- Nagano J, Kono S, Preston DL, Mabuchi K. (89) 2001 Green Not supportive
Subjects were 38,540 people (14,873 men, mean age 52.8 years; 23,667 women, mean age 56.8 years) who responded to *a mail survey carried out between 1979 and 1981*. The study analyzed solid cancers (n = 3881); hematopoietic cancers (188); cancers of all sites combined (4069); and cancer of specific sites with more than 100 cases, i.e. stomach (901), colon (432), rectum (193), liver (418), gallbladder (122), pancreas (122), lung (436), breast (281), and bladder (122). Poisson regression was used to allow for city, gender, age, radiation exposure, smoking status, alcohol drinking, body-mass index, education level, and calendar time. RESULTS: Green tea consumption was virtually unrelated to incidence of cancers under study. The relative risks of all cancers for those consuming green tea twice to four times per day and five or more times per day were 1.0 (95% confidence interval 0.91-1.1) and 0.98 (0.88-1.1), respectively, as compared with those consuming green tea once per day or less. CONCLUSION: *Our findings do not provide evidence that regular green tea consumption is related to reduced cancer risks. This failure may be due to some crudeness in the assessment of green tea intake; green tea consumption was determined only in terms of*

self-reported daily frequency of drinking, and the highest category was five or more cups per day. Bioactivity of a cup of green tea obviously differs by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the pot. In Shizuoka prefecture, which has the highest production of green tea leaves in Japan, residents of towns with low mortality from stomach cancer were found not only to drink green tea more frequently, but also to renew tea leaves more frequently than those of a town with high mortality from stomach cancer.

References (1-135) with relevant abstract attached to each title.

1. Agudo A, Gonzalez CA, Marcos G, Sanz M, Saigi E, Verge J, Boleda M, Ortego J. Consumption of alcohol, coffee, and tobacco, and gastric cancer in Spain. *Cancer Causes Control*. 1992 Mar;3(2):137-43.

A case-control study on gastric cancer was carried out between 1987 and 1989 in four regions of Spain. Three hundred and fifty-four cases of histologically confirmed adenocarcinoma were included (235 men and 119 women). For each case, a control was selected, matched by sex, age, and area of residence, from the same hospital as the case. No association was observed with smoking, nor with the consumption of coffee or tea. The usual consumption of alcohol was associated with gastric cancer in men (odds ratio = 1.54, 95 percent confidence interval = 1.03-2.31), but there was no dose-response relationship. No association was observed in women. All estimations were carried out taking into account the effect of the dietary factors associated with gastric cancer. In accordance with previous evidence, the association observed between gastric cancer and alcohol appears not to be causal.

2. Armstrong B, Garrod A, Doll R. A retrospective study of renal cancer with special reference to coffee and animal protein consumption. *Br J Cancer*. 1976 Feb;33(2):127-36.

Interviews were obtained with 106 patients with adenocarcinoma of the renal parenchyma, 33 patients with carcinoma of the renal pelvis and 139 individually matched control patients. Comparison of the cancer patients with the control patients showed no evidence of a positive association between either type of renal cancer and coffee or animal protein consumption. Carcinoma of the renal pelvis was associated positively with cigarette consumption (relative risk estimate 1-8) and the daily consumption of analgesic tablets was more frequent in patients with cancer of the renal parenchyma than in their matched controls (14-2% compared with 1-9%, P less than 0.005). It appeared likely that the latter relationship was non-causal.

3. Arts IC, Hollman PC, Bueno De Mesquita HB, Feskens EJ, Kromhout D. Dietary catechins and epithelial cancer incidence: the Zutphen elderly study. *Int J Cancer*. 2001 Apr 15;92(2):298-302.

The flavonoids, a group of more than 4,000 polyphenolic antioxidants, are potential cancer preventive components of fruits and vegetables. Catechins, one of the 6 major groups of flavonoids, are present in high concentrations in tea as well. Our objective was to evaluate the association between intake of catechins and incidence of epithelial cancers with data from the Zutphen Elderly Study, a prospective cohort study among 728 men aged 65-84 years in 1985. The average catechin intake at baseline was 72 mg/day (range, 0-355 mg/day). After 10 years of follow-up, 96 incident epithelial cancers were recorded, including 42 cases of lung cancer. After multivariate adjustment, catechin intake was not associated with epithelial cancer (risk ratio [RR] from lowest to highest tertile: 1.00, 0.75, 0.94; p for trend: 0.82), or lung cancer (RR from lowest to highest tertile: 1.00, 0.72, 0.92; p for trend: 0.80). Catechins not from tea were borderline significantly inversely associated with lung cancer incidence (RR and 95% confidence interval [CI] for a 7.5-mg increase in intake: 0.66, 0.42-1.05), whereas catechins

from tea were not. Catechins from apple, the major source of non-tea catechins, were also related to lung cancer incidence (RR and 95% CI for a 7.5-mg catechin increase: 0.67, 0.38-1.17). Because tea, the major catechin source in this population, was not associated with cancer risk, it seems unlikely that catechins are responsible for the observed inverse trend between non-tea catechins and lung cancer incidence. However, differences in bioavailability of the various catechins may play a role; effects on individual cancer sites cannot be excluded and merit further investigation. Copyright 2001 Wiley-Liss, Inc.

4. Baron JA, Gerhardsson de Verdier M, Ekblom A. Coffee, tea, tobacco, and cancer of the large bowel. *Cancer Epidemiol Biomarkers Prev.* 1994 Oct-Nov;3(7):565-70.
Cancer Epidemiology Unit, Uppsala University, Sweden.

The impact of tobacco use and coffee and tea intake on the risk of colorectal cancer is unclear. Previous research has suggested that coffee may be protective against these cancers, and investigation regarding tea or cigarette smoking has yielded inconsistent results. To clarify these issues, we evaluated coffee and tea intake and tobacco smoking as risk factors for cancer of the colon and rectum in a population-based case-control study from Stockholm, Sweden. Cases were ascertained from the regional cancer registry, and controls identified through population registers. Subjects completed a questionnaire requesting information regarding foods and beverages consumed, exercise, tobacco use, and personal characteristics. Logistic regression modelling was used to compute odds ratios. A total of 352 cases of colon cancer, 217 cases of rectal cancer, and 512 controls took part. High coffee intake was negatively associated with the risk of colon cancer: the odds ratio for those drinking 6 or more cups per day was 0.55 (95% confidence interval, 0.31-0.96) compared to those drinking one or fewer. There was no association with rectal cancer. For tea, the associations were the opposite: there was no association with colon cancer risk, but the odds ratio for rectal cancer was 0.56 (95% confidence interval, 0.34-0.90) for those drinking 2 or more cups per day compared with those drinking none. Smokers of 11 or more cigarettes per day had a 20 to 30% reduction in the risk of colon and rectal cancer, but these findings were consistent with chance. There was no association of long-term cigarette smoking with risk.

5. Bianchi GD, Cerhan JR, Parker AS, Putnam SD, See WA, Lynch CF, Cantor KP. Tea consumption and risk of bladder and kidney cancers in a population-based case-control study. *Am J Epidemiol.* 2000 Feb 15;151(4):377-83.

Department of Preventive Medicine and Environmental Health, The University of Iowa College of Medicine, Iowa City, USA.

Recent epidemiologic studies have suggested that tea may be protective against cancers of the urinary tract. The authors examined the association between usual adult tea consumption and risk of bladder and kidney cancers in a population-based case-control study that included 1,452 bladder cancer cases, 406 kidney cancer cases, and 2,434 controls. For bladder cancer, the age- and sex-adjusted odds ratios (OR) (95% confidence intervals (CI)) referent to nonusers of tea were 0.9 (0.7, 1.1) for <1.0 cup/day, 1.0 (0.8, 1.2) for 1.0-2.6 cups/day, and 0.9 (0.7, 1.1) for >2.6 cups/day (cutpoints for users based on the tertile distribution among controls). When more

extreme cutpoints were used, persons who consumed >5 cups/day (>90th percentile) had a suggestive decreased risk (OR = 0.7; 95% CI 0.5, 1.0), but there was no evidence of a dose-response relation. In analyses stratified by median total beverage intake (2.6 liters/day), there was an inverse association with tea use among persons who consumed less than the median (OR = 0.5; 95% CI 0.3, 0.8) but no association for persons who consumed at or above the median. In contrast, for kidney cancer, there was no association with tea use. Adjustment for site-specific risk factors did not alter these results. This study offers only minimal support for an inverse association between tea consumption and bladder or kidney cancer risk.

6. Blot WJ, McLaughlin JK, Chow WH. Cancer rates among drinkers of black tea. *Crit Rev Food Sci Nutr*. 1997 Dec;37(8):739-60.

International Epidemiology Institute, Rockville, MD 20850, USA.

Studies in experimental animals have shown that compounds in tea can inhibit the process of carcinogenesis, with the beneficial effects accruing to both green and black teas. Herein epidemiologic studies around the world are reviewed to assess the rates and risks of cancer among black tea drinkers. Ecologic data suggest at most a modest benefit on total cancer, as there is considerable international variation in black tea consumption but generally small differences in overall cancer rates. Cohort studies of tea drinkers and case control studies of specific cancers show mixed results. Consistent dose-related patterns have yet to emerge, although detailed data from these studies on cancer risks according to amount and duration of black tea intake are often limited. Several investigations point to the possibility of somewhat lowered risks of digestive tract cancers among tea drinkers, but the evidence is inconclusive. Further research, especially involving populations with wide ranges of tea consumption, is needed to clarify black tea's impact on cancer risk.

7. Bruemmer B, White E, Vaughan TL, Cheney CL. Fluid intake and the incidence of bladder cancer among middle-aged men and women in a three-county area of western Washington. *Nutr Cancer*. 1997;29(2):163-8.

Division of Clinical Research, Fred Hutchinson Cancer Research Center, Seattle, WA, USA.

This population-based case-control study reports on the relationship between fluid intake and the incidence of bladder cancer among 262 bladder cancer cases from Western Washington and 405 controls identified through random-digit dialing. Cases were identified from the Surveillance, Epidemiology, and End Results (SEER) registry and were diagnosed between January 1987 and June 1990. All eligible subjects were Caucasian 45- to 65-year-old residents of King, Pierce, or Snohomish counties and completed a structured telephone interview. Analyses were conducted by logistic regression with adjustment for age, county, and smoking (current, former, never). Among women there was a positive association between total fluid intake and the incidence of bladder cancer [p (trend) = 0.02] and a moderate positive association between the use of decaffeinated coffee and the incidence of bladder cancer [p (trend) = 0.08]. Among men there was an inverse association between the consumption of regular soft drinks and the incidence of bladder cancer [p (trend) = 0.03]. No association was found between the incidence of bladder cancer and the intake of water, coffee, tea, diet soft drinks, alcohol, or liquids from tap for men.

or women. This study suggests that the intake of water and specific beverages is overall not associated with risks of bladder cancer. This study provides limited evidence of a positive association between total fluid intake and bladder cancer among women.

8. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P.

Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer*. 1992 Feb 20;50(4):514-22.

From 1984 to 1988 a population-based case-control study was carried out in the Netherlands, in collaboration with the International Agency for Research on Cancer, to examine the possible relationship between the habitual lifetime consumption of alcohol, coffee and tea and exocrine pancreatic carcinoma in 176 cases and 487 controls. An interviewer-administered questionnaire was used to ascertain major life events and obtain estimates of consumption (ever-never) and frequency of consumption throughout life. Logistic regression analyses yielded odds ratios adjusted for age, sex, response status, smoking, dietary intake of energy and vegetables and of alcoholic or non-alcoholic drinks. When compared with data from non-drinkers, the cumulative lifetime consumption of all types of alcohol in grams of ethanol (ORs 1.00, 0.97, 0.93, 1.25, *p* trend 0.55), beer, spirits, red wine and fortified wine was not related to risk. The consumption of white wine was inversely associated with risk (OR 0.41, 95% CI 0.24-0.70). The uniformly reduced risk estimates for the lifetime number of drinks of white wine were based on small numbers (ORs 1.00, 0.44, 0.25, 0.40, *p* trend 0.001). When compared with data from non-drinkers, our findings suggest an inverse dose-response relationship for the lifetime consumption of coffee (ORs 1.00, 0.72, 0.37, 0.58, *p* trend 0.06), whereas lifetime consumption of tea and of ground, instant and decaffeinated coffee was not associated with risk. The absence of an effect of lifetime consumption of decaffeinated coffee may be due to the small numbers of subjects. These results further strengthen existing evidence against a positive association between consumption as well as lifetime consumption of (sources of) alcohol, tea or coffee and the development of exocrine pancreatic cancer.

9. Castelletto R, Castellsague X, Munoz N, Iscovich J, Chopita N, Jmelnitsky A.

Alcohol, tobacco, diet, mate drinking, and esophageal cancer in Argentina. *Cancer Epidemiol Biomarkers Prev*. 1994 Oct-Nov;3(7):557-64.

To study the role of hot mate drinking, alcohol, tobacco, and diet in esophageal cancer, a case-control study including 131 cases and 262 hospital controls was carried out in La Plata, Argentina. In multivariate analyses, statistically significant increases in risk were detected for alcohol, tobacco, and some dietary factors but not for hot mate drinking. A strong dose-response relationship was observed with the amount of alcohol consumed daily but not with the number of cigarettes smoked. The odds ratio for those drinking more than 200 ml of ethanol/day compared to nondrinkers was 5.7 (95% confidence interval, 2.2-15.2). An increased risk was also observed for those eating barbecued meat more than once a week (odds ratio, 2.4; 95% confidence interval, 1.2-4.8) as compared to those eating it less than once a week, and a reduction in risk was associated with daily consumption of nonbarbecued beef as compared to those eating it less than daily. Concerning mate drinking, the only variable that showed an effect was the

temperature at which mate is drunk. Those who reported drinking mate hot or very hot as compared to those drinking it warm had an increase in risk (odds ratio, 1.7; 95% confidence interval, 1.0-2.9). Our findings strengthen the evidence for an important role of alcohol and tobacco in esophageal carcinogenesis but do not provide strong support for a role of hot mate drinking.

10. Castellsague X, Munoz N, De Stefani E, Victora CG, Castelletto R, Rolon PA. Influence of mate drinking, hot beverages and diet on esophageal cancer risk in South America. *Int J Cancer*. 2000 Nov 15;88(4):658-64.

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To estimate the effects of consuming hot beverages, including mate (an infusion of the herb *Ilex paraguayensis*), tea, coffee and coffee with milk, and other food items on esophageal cancer risk, we analyzed data from 830 cases and 1,779 controls participating in a series of 5 hospital-based case-control studies of squamous-cell carcinoma of the esophagus conducted in high-risk areas of South America. After adjusting for the strong effects of tobacco and alcohol consumption, both heavy mate drinking (>1 l/day) and self-reported very hot mate drinking were significantly associated with esophageal cancer risk in men and women. The magnitude and strength of the association for mate amount and, to a lesser extent, mate temperature were higher for women than men. The joint effects of mate amount and mate temperature were more than multiplicative, following a statistically significant synergistic interaction ($p = 0.02$) which was particularly evident among heavy drinkers (>1.50 l/day) of very hot mate (odds ratio = 4.14, 95% confidence interval: 2.24-7.67) compared to light drinkers (<0.50 l/day) of cold/warm/hot mate.

Consumption of other very hot beverages, such as tea and coffee with milk but not coffee alone, was also significantly associated with an increased risk, in the 2- to 4-fold range. Statistically significant protective associations were identified for high consumption of vegetables, fruits, cereals and tea. In contrast, frequent consumption of meat, animal fats and salt was associated with a moderately increased risk. This pooled analysis adds evidence for a carcinogenic effect of chronic thermal injury in the esophagus induced by the consumption of very hot drinks, including mate. Our study further confirms the protective effect of a dietary pattern characterized by daily consumption of fruits and vegetables and low consumption of meat and animal fats.

11. Cheng KK, Day NE. Nutrition and esophageal cancer. *Cancer Causes Control* 1996 Jan;7(1):33-40.

Epidemiologic evidence on the relation between nutrition and esophageal cancer is reviewed. Results from ecologic, case-control, cohort, and intervention studies are included. Most of the findings pertain more to squamous cell carcinoma than adenocarcinoma of the esophagus. The protective effect of fruit and vegetable consumption is supported by a large body of evidence, especially from case-control studies. The effects of food groups and nutrients other than fruits and vegetables also have been examined, but the overall evidence is less convincing. Recent intervention studies in high incidence areas in China indicate that micronutrient supplements may have a modest effect in reducing risk, but the generalizability of this result is uncertain. Hot drinks are likely to increase the risk of esophageal cancer. On the other hand, the role of tea drinking, especially the use of green tea, remains to be defined better.

12. Chow WH, Swanson CA, Lissowska J, Groves FD, Sobin LH, Nasierowska-Guttmejer A, Radziszewski J, Regula J, Hsing AW, Jagannatha S, Zatonski W, Blot WJ. Risk of stomach cancer in relation to consumption of cigarettes, alcohol, tea and coffee in Warsaw, Poland. *Int J Cancer*. 1999 Jun 11;81(6):871-6.

Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA. choww@exchange.nih.gov. To identify reasons for the high incidence rates of stomach cancer in Poland, we conducted a population-based case-control study in Warsaw. Cases were residents aged 21 to 79 years who were newly diagnosed with stomach cancer between March 1, 1994, and April 30, 1997. Controls were randomly selected from Warsaw residents registered at the nationwide Polish Electronic System of Residence Evidency, frequency-matched to cases by age and sex. Information on demographic characteristics; consumption of cigarettes, alcohol, tea and coffee; diet; medical history; family history of cancer; occupational history; and living conditions during adolescence was elicited by trained interviewers using a structured questionnaire. Included were 464 cases (90% of eligible) and 480 controls (87% of eligible). Among men, the risk of stomach cancer was significantly elevated among current smokers (OR = 1.7, 95% CI = 1.1-2.7) but not among former smokers. The excess risk was largely confined to long-term and heavy smokers, with significant 2-fold excess risk among men who smoked 40 or more pack-years. Among women, an 80% increase in risk was observed in both current and former smokers but dose-response trends were less consistent than among men. Alcohol consumption was not clearly related to risk, and no association was found for drinking regular coffee or herbal tea or using milk/cream in coffee or tea. A significant reduction in risk was linked to daily tea drinking among women, but not among men. Our findings confirm an association with cigarette smoking, which is estimated to account for approximately 20% of stomach cancers diagnosed among Warsaw residents during the study period.

13. Claude J, Kunze E, Frentzel-Beyme R, Paczkowski K, Schneider J, Schubert H. Life-style and occupational risk factors in cancer of the lower urinary tract. *Am J Epidemiol*. 1986 Oct;124(4):578-89.

In a matched case-control study of cancer of the lower urinary tract in northern Germany in which 340 male and 91 female case-control pairs were interviewed between 1977 and 1982, cigarette smokers were found to have an odds ratio of 2.3 for males and 2.9 for females compared with nonsmokers. A significant dose-response relation was observed for increasing cigarette consumption, and a significant decrease in risk was shown for ex-smokers. Employment in rubber, plastics, dye, textiles, and mining industries was associated with a higher risk, and increased odds ratios were also observed for exposure to spray painting, coal pitch, chromium, and zinc. Controlling for smoking, an elevated risk of 2.3 for drinking more than four cups of coffee per day and significant odds ratios of 2.1 and 2.8 for a daily consumption of 0.5-1.0 liter and above 1.0 liter of beer, respectively, were noted among men. A highly significant odds ratio of 4.0 was found for a daily fluid intake of more than 2 liters. Dietary habits such as the frequent consumption of canned food and fatty meals were associated with a higher risk, whereas a regular consumption of fruits and vegetables was associated with a lower risk. Fourteen determinants found to be important in this case-control series were analyzed by using multiple logistic regression.

14. Cook-Mozaffari PJ, Azordegan F, Day NE, Ressicaud A, Sabai C, Aramesh B. Oesophageal cancer studies in the Caspian Littoral of Iran: results of a case-control study. *Br J Cancer*. 1979 Mar;39(3):293-309.

The purpose was to study factors identified in a previous study as potentially causally related to cancer of the oesophagus. Other tumours (lung, stomach, breast, large bowel, larynx and pharynx) were included to distinguish findings specific for oesophageal cancer from general characteristics of cancer patients, due for example to ascertainment bias, and to verify that expected associations, such as between lung cancer and cigarette smoking, would emerge under the prevailing field conditions. Two controls were chosen per case, matched for village of residence, age, sex and language group. Reinterviewing was performed to a limited extent to assess the accuracy of replies to questionnaires. The following were found not to be associated with oesophageal cancer: consumption of sheep's milk and yoghurt, sesame oil, chewing of nass, making of carpets, use of pregnancy diets, salting and sun-drying of meat and use of wild spinach. The use of opium, bread and tea could not be assessed in the retrospective framework. Strongly associated with risk of oesophageal cancer were low socio-economic status and low intake of fresh fruit and vegetables. The two factors each had an independent effect, and were more marked for oesophageal cancer than for the other tumours.

15. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer*. 1989 Mar 15;43(3):415-21.
Department of Mathematics, Statistics and Epidemiology, Imperial Cancer Research Fund, Lincoln's Inn Fields, London, UK.

A case-control study comprising 216 cases of pancreatic cancer and 279 controls was conducted to investigate the relationship of pancreatic cancer with certain chronic medical conditions and with the consumption of tea, coffee and alcoholic beverages. Significant positive associations with pre-existing diabetes mellitus and gall-bladder disease were observed and there was weak evidence of association with liver disease. The relative risks for diabetes mellitus and gallstones diagnosed at least one year previously were 4.1 ($p = 0.005$) and 2.8 ($p = 0.01$) respectively. Cases drank significantly more beer than controls ($p = 0.005$) and there was evidence of a positive trend in risk with total alcohol consumption. Smoking was a clear risk factor, but cases and controls were very similar with respect to tea and coffee drinking habits.

16. De Jong UW, Breslow N, Hong JG, Sridharan M, Shanmugaratnam K. Aetiological factors in oesophageal cancer in Singapore Chinese. *Int J Cancer*. 1974 Mar 15;13(3):291-303.

PIP: Analysis of a hospital-based case-control study of esophageal cancer among Singapore Chinese (composed of Cantonese, Hokkien, Teochew, and other dialect groups) revealed the following statistically significant risk factors for both sexes: 1) belonging to either Hokkien or Teochew dialect group; 2) consuming beverages at temperatures stated subjectively to be burning hot before illness; and 3) smoking Chinese cigarettes. Additional risk factors for males were birth in China and consumption of Samsu (Chinese wine). Bread, potato, and banana consumption was reported at significantly lower levels in male esophagus cancer patients than

controls. Esophageal cancer was less common in males who attended school for more than 8 years. Multivariate analysis (joint influence of selected variables) confirmed the strong effects of dialect group and beverage temperature for both sexes. For females, Chinese cigarette smoking remained a risk factor; for males, Samsu consumption. Smoking western cigarettes and drinking strong liquors were not significantly related for either sex. These findings suggest that esophageal cancer is more likely to occur among traditional Chinese who maintain dietary patterns which include Samsu and scalding beverages but avoid bland foodstuffs not native to the culture. The greater risk in Teochew and Hokkien may be due in part to beverage temperature, since "burning hot" was cited more frequently in these dialect groups. However, these differences are based on subjective impressions and require further verification.

17. Demirer T, Icli F, Uzunalimoglu O, Kucuk O. Diet and stomach cancer incidence. A case-control study in Turkey. *Cancer* 1990 May 15;65(10):2344-8.

A case-control study of diet and stomach cancer was conducted in Ankara, Turkey, between December 1987 and March 1988. One hundred patients with adenocarcinoma of the stomach were matched with 100 control subjects according to age, sex, and residential area. A dietary questionnaire was administered to all subjects by one of the authors. Gastric cancer patients consumed less fresh fruit and yellow-green vegetables (P less than 0.0001) and meats (P less than 0.001), and more salted food (P less than 0.001), condiments (P less than 0.0001), and salt (P less than 0.001) compared with the control group. Twenty-four percent of the gastric cancer patients and 4% of the groups with regard to the consumption of starches, fried foods, cereals, milk, dairy products, tea, alcohol, and tobacco. Stomach cancer patients brushed their teeth less frequently (P less than 0.0001) and had more deficient teeth (P less than 0.0001) compared with the control group.

18. Ellison LF. Tea and other beverage consumption and prostate cancer risk: a Canadian retrospective cohort study. *Eur J Cancer Prev.* 2000 Apr;9(2):125-30.
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Using participants in the 1970-1972 Nutrition Canada Survey (NCS), a retrospective cohort study was conducted to assess the relationship between tea, as well as coffee, cola and alcohol, and the risk of developing prostate cancer. The mortality and cancer experience of male NCS participants aged 50-84 years was determined up to 31 December 1993. Among the 3400 survey participants included in the study, 145 developed prostate cancer. No association was observed between tea (predominantly black tea) intake and prostate cancer. Subjects who drank more than 500 ml of tea per day experienced virtually the same risk as those who reported no tea consumption (rate ratio (RR) 1.02, 95% confidence interval (CI) 0.62-1.65). Compared to those who reported no coffee drinking, men who averaged more than 250-ml per day experienced a 40% increase in risk (95% CI 0.84-2.32). Cola consumption was not associated with an increased risk of prostate cancer. Total alcohol consumption was not related to subsequent development of prostate cancer, although very moderate consumption of wine (< 10 g per day), relative to no consumption, showed an RR of 1.48 (95% CI 1.05-2.09). These data do not support an association between consumption of tea and prostate cancer risk.

19. Ewertz M, Gill C. Dietary factors and breast-cancer risk in Denmark. *Int J Cancer*. 1990 Nov 15;46(5):779-84.

Danish Cancer Registry, Institute of Cancer Epidemiology, Copenhagen.

The influence of dietary factors, in particular the intake of fat and beta-carotene, on breast-cancer risk was evaluated in a case-control study including 1,486 breast cancer cases diagnosed over a 1 year period in Denmark. The control group was an age-stratified random sample of 1,336 women from the general population. Data on usual diet prior to the breast cancer diagnosis were collected by self-administered questionnaires of the semi-quantitative food frequency type. A highly significant trend (p less than 0.001) of increasing risk was observed with increasing fat intake, the RR for the highest quartile being 1.45 (95% CI 1.17-1.80) compared with the lowest. However, information was not available to allow adjustment for the possible confounding effect of energy intake. The risk of breast cancer was not associated with consumption of vegetables rich in beta-carotene, multi-vitamin tablets or other dietary supplements, coffee, tea, sugar or artificial sweeteners.

20. Fujiki H, Suganuma M, Imai K, Nakachi K. Green tea: cancer preventive beverage and/or drug. *Cancer Lett* 2002;188:9-13.

Department of Biochemistry, Faculty of Pharmaceutical Sciences, Tokushima Bunri, University, Yamashiro-cho, 770-8514, Tokushima, Japan.

Green tea and (-)-epigallocatechin gallate (EGCG) are now acknowledged cancer preventives in Japan and has made it possible for us to establish the concept of a cancer preventive beverage. For the general population, we recommend 10 cups of green tea daily supplemented with green tea tablets. For cancer patients following treatment, we here present new evidence that green tea and a cancer preventive drug, sulindac, have synergistic preventive effects. An approach to develop green tea capsules as a cancer preventive drug in the US is discussed, aiming at taking full advantage of this cancer preventive beverage.

21. Fujiki H, Suganuma M, Okabe S, Sueoka E, Sueoka N, Fujimoto N, Goto Y, Matsuyama S, Imai K, Nakachi K. Cancer prevention with green tea and monitoring by a new biomarker, hnRNP B1. *Mutat Res* 2001;480-481:299-304.

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The study of green tea polyphenols as a cancer preventative is approaching a new era, with significant results accumulating rapidly. This paper briefly reviews four topics related to mechanisms of action of tea polyphenols: (I) identification of the genes commonly affected by EGCG, as demonstrated by Clontech's Atlas cDNA Expression Array; (II) the significance of heterogeneous nuclear ribonucleoprotein B1 (hnRNP B1) as a new biomarker for early detection of lung cancer, and inhibition of its expression by EGCG; (III) the synergistic or additive effects of EGCG with the cancer preventive agents, sulindac and tamoxifen, on induction of apoptosis in PC-9 cells and on inhibition of intestinal tumor development in multiple intestinal neoplasia (Min) mice; (IV) the results of a 10 year prospective cohort study demonstrating the

effectiveness of daily consumption of green tea in preventing cancer, and a prototype study for developing green tea beverage as cancer preventive.

22. Galanis DJ, Kolonel LN, Lee J, Nomura A. Intakes of selected foods and beverages and the incidence of gastric cancer among the Japanese residents of Hawaii: a prospective study. *Int J Epidemiol.* 1998 Apr;27(2):173-80.

Cancer Research Center of Hawaii, University of Hawaii, Honolulu, USA.

BACKGROUND: We report on the associations between the intake of certain foods and beverages and the incidence of gastric cancer in a cohort of 11,907 randomly selected Japanese residents of Hawaii (6297 women and 5610 men). **METHODS:** The daily intake of six beverages, cigarettes and alcohol and the weekly frequency of intake of 13 foods and food groups was estimated with a short food frequency questionnaire. Over an average follow-up period of 14.8 years, 108 cases of gastric cancer (44 women, 64 men) were identified via linkage to the Hawaii Tumor Registry. **RESULTS:** In gender-combined proportional hazards analyses, the consumption of fresh fruit seven or more times per week was associated with a significantly reduced risk of gastric cancer, compared to lower levels of consumption (relative hazard (RH): 0.6, 95% confidence interval (CI): 0.4-1.0, $P = 0.03$). The combined intake of fresh fruit and raw vegetables was inversely associated with the risk of gastric cancer in the total cohort, and among the men ($P < 0.05$). No significant relationships were found between gastric cancer incidence and the intake of pickled vegetables, miso soup, dried or salted fish, or processed meats among either gender. Compared to non-drinkers, men who drank one cup of coffee per day had a significantly elevated risk of gastric cancer (RH: 2.5, 95% CI: 1.0-6.1, $P = 0.05$), but there was no evidence of a dose-response relationship. Cigarette smoking and consumption of alcohol were not related to gastric cancer, in analyses restricted to the men. **CONCLUSIONS:** The results related to fruit and vegetable intake are consistent with an anti-nitrosating effect of these foods, while the unexpected association between coffee consumption and gastric cancer is difficult to explain and may represent a chance finding.

23. Galanis DJ, Lee J, Kolonel LN. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer.* 1997 May 1;79(9):1840-1.

In a Correspondence on: *Cancer.* 1996 Jun 15;77(12):2449-57. The authors questioned the effectiveness of green tea in chemoprevention of stomach cancer.

24. Gao YT, McLaughlin JK, Blot WJ, Ji BT, Dai Q, Fraumeni JF Jr. Reduced risk of esophageal cancer associated with green tea consumption. *J Natl Cancer Inst* 1994 Jun 1;86(11):855-8.

BACKGROUND: Studies in laboratory animals have suggested inhibitory effects of green tea on the induction of some cancers, notably, esophageal cancer. However, only a few epidemiologic studies have evaluated green tea as a potential inhibitor of human esophageal cancer. **PURPOSE:** Our purpose was to evaluate the relationship between green tea consumption and the risk of esophageal cancer. **METHODS:** This esophageal cancer study was part of a larger multicenter,

case-control study that included three other gastrointestinal sites (pancreas, colon, and rectum). Medical records of patients aged 30-74 years old who were diagnosed with esophageal cancer from October 1, 1990, through January 31, 1993, were identified from the Shanghai Cancer Registry, which covers 6.8 million people in the urban area of Shanghai, People's Republic of China. During the ascertainment period, records of 1016 eligible cases of esophageal cancer were identified. Control subject records were selected by frequency matching in accordance with the age-sex distribution of the four gastrointestinal cancers ascertained by the cancer registry during 1986-1987. Patient interviews were then conducted using a structured, standardized questionnaire to obtain information on demographic characteristics, residential history, height and weight, diet, smoking, alcohol and tea drinking, medical history, family history of cancer, occupation, physical activity, and reproductive history. RESULTS: Of the 902 patients interviewed, 734 (81.4%) had their disease pathologically confirmed. There were 1552 control subjects interviewed, including 240 alternates. All analyses of tea effects were conducted separately among men and women and all were adjusted for age. After further adjustment for other known confounders, a protective effect of green tea drinking on esophageal cancer was observed among women (odds ratio [OR] = 0.50; 95% confidence interval [CI] = 0.30-0.83), and this risk decreased (P for trend $\leq .01$) as tea consumption increased. Among men, the ORs were also below 1.00, although not statistically significant. ORs for green tea intake were estimated among those persons who neither smoked nor drank alcohol. In this subset, statistically significant decreases in risk among tea drinkers were observed for both men (OR = 0.43; 95% CI = 0.22-0.86; P for trend = .05) and women (OR = 0.40; 95% CI = 0.20-0.77; P for trend $< .001$). CONCLUSIONS: This population-based, case-control study of esophageal cancer in urban Shanghai suggests a protective effect of green tea consumption. Although these findings are consistent with studies in laboratory animals, indicating that green tea can inhibit esophageal carcinogenesis, further investigations are definitely needed.

25. Goldbohm RA, Hertog MG, Brants HA, van Poppel G, van den Brandt PA. Consumption of black tea and cancer risk: a prospective cohort study. *J Natl Cancer Inst* 1996 Jan 17;88(2):93-100.

BACKGROUND: Tea is one of the most frequently consumed beverages in the world. Antioxidant polyphenol compounds (such as catechins and flavonols) are abundantly present in both green and black teas and have been observed to have anticarcinogenic properties in cell and animal model studies. In black tea, however, most of the catechins have been oxidized to forms that may have reduced anticarcinogenic properties. Despite indications from experimental studies that tea may protect against cancer, epidemiologic evidence has been inconclusive.

PURPOSE: The association between black tea consumption and the subsequent risk of stomach, colorectal, lung, and breast cancers was investigated in The Netherlands Cohort Study on Diet and Cancer among 58,279 men and 62,573 women aged 55-69 years. METHODS: Subjects in the cohort completed a self-administered questionnaire on dietary habits and other risk factors for cancer at base line in 1986. Follow-up for cancer was done by means of computerized record linkage with all nine regional cancer registries in The Netherlands and the national pathology database. During 4.3 years of follow-up, 200, 650, 764, and 650 cases of stomach, colorectal, lung, and breast cancers were diagnosed, respectively. The questionnaire data of case subjects and those of a random subcohort ($n = 3500$) were used to calculate rate ratios (RRs) of cancer in

categories of consumers of black tea compared with nonconsumers. RESULTS: Tea was not used by 13% of the subjects in the cohort, whereas 37%, 34%, and 16% consumed one to two, three to four, and five or more cups of tea per day, respectively. No association was observed between tea consumption and risk of colorectal cancer: The risk among tea drinkers in each consumption category was similar to that among nondrinkers. The RR of breast cancer among consumers of five or more cups of tea per day was 1.3 (95% confidence interval = 0.9-2.0); no dose-response association was observed. In age- and sex-adjusted analyses, consumption of tea was inversely associated with stomach (two-sided P for trend = .147) and lung (two-sided P for trend < .001) cancers. However, tea drinkers appeared to smoke less and to eat more vegetables and fruits than nondrinkers. When smoking and dietary factors were taken into account, tea in itself did not appear to protect against stomach and lung cancers: The RRs in all consumption categories were close to unity. Analysis of the tea and cancer relationship in a subgroup that included subjects in the lowest two quintiles of consumption of vegetables and fruits also failed to reveal a protective effect of tea consumption on the risk of three cancer types studied (colorectal, lung, and breast cancers). CONCLUSIONS: This investigation does not support the hypothesis that consumption of black tea protects against four of the major cancers in humans; a cancer-enhancing effect was not evident, either.

26. Goodman MT, Morgenstern H, Wynder EL. A case-control study of factors affecting the development of renal cell cancer. *Am J Epidemiol.* 1986 Dec;124(6):926-41.

A hospital-based case-control study was conducted between 1977 and 1983 of 189 men and 78 women with renal cell carcinoma at 18 hospital centers in six US cities and an equal number of controls matched on the basis of hospital, sex, race, age (± 5 years), and time of admission (± 12 months). Quetelet index (weight/height²) was found to be associated with renal cell cancer in both men and women. Crude odds ratios (ORs) for individuals in the upper tertile of the Quetelet index distribution (28 or more) were calculated to be 2.7 (95% confidence interval (CI) = 1.5-5.9) among men and 2.4 (95% CI = 1.2-6.8) among women compared to the lowest tertile. This relationship was found to be independent of the effects of cigarette smoking, chewing tobacco use, and decaffeinated coffee consumption. The use of chewing tobacco among men was positively associated with disease (OR = 4.0; 95% CI = 1.2-12.9). This was due primarily to a significant interaction between chewing tobacco use and cumulative cigarette smoking. The fitted odds ratio for persons who chewed tobacco and had 30 pack-years of cigarette smoke exposure, compared to never users of either tobacco product, was 26.0 (95% CI = 4.4-153.0) after adjusting for Quetelet index and decaffeinated coffee use. The odds ratio for decaffeinated coffee consumption among men and women combined was 1.9 (95% CI = 1.0-3.8) after controlling for other risk factors. A consistent dose-response was not found, however, by number of cups of decaffeinated coffee consumed per day. Those drinking 1-2 cups had an odds ratio of 2.0 while those drinking 3 cups or more per day had an odds ratio of 1.3, thus casting doubt on a causal interpretation of the finding. Alcohol drinkers had a lower, although not significantly different, rate of renal cell cancer than did never drinkers when the data were examined separately by sex. However, combining the data for both sexes yielded a crude odds ratio of 0.6 (95% CI = 0.4-1.0) for this association. There was no independent effect of tobacco smoking on the odds ratio for renal cell cancer. No significant differences between cases and controls were found for either the amount or duration of artificial sweetener use or the lifetime consumption of

saccharin. Beverages such as caffeinated coffee, soft drinks, and tea, in addition to physical activity and occupation, were unrelated to the occurrence of disease.

27. Goto R, Masuoka H, Yoshida K, Mori M, Miyake H. A case control study of cancer of the pancreas *Gan No Rinsho* 1990 Feb;Spec No:344-50 [Article in Japanese]

We report the findings of a case-control study of cancer of the pancreas, which was conducted in Hokkaido Prefecture. Seventy-one patients with pancreatic cancer were matched on sex and age (± 3 years) to 142 community-based controls. The latter had telephone interviews. We questioned all subjects about demographic factors, diet, beverage consumption, and medical and surgical history. Significantly decreased risks were associated with consumption of raw vegetables and green tea. The risk increased significantly with consumption of the fat of meat, boiled fish, coffee, black tea and alcoholic beverages.

28. Gupta S, Ahmad N, Mukhtar H. Prostate cancer chemoprevention by green tea. *Semin Urol Oncol.* 1999 May;17(2):70-6.

Prostate cancer (PCA) is one of the most invasive cancers and the second leading cause of cancer-related deaths among males in the United States. According to an estimate, 1 of every 11 American men will eventually develop PCA. One way to reduce the occurrence of cancer is through chemoprevention. PCA represents an excellent candidate disease for chemoprevention because it is typically diagnosed in men over 50 years of age, and therefore even a modest delay in neoplastic development achieved through pharmacological or nutritional intervention could result in a substantial reduction in the incidence of clinically detectable disease. The ideal agent(s) suitable for chemoprevention of PCA should be the one(s) that has proven efficacy in the laboratory experiments on one hand, and also possesses proven epidemiological basis on the other hand. This review attempts to address the issue of possible uses of tea, especially green tea, for the prevention of PCA. We are providing the experimental as well as the epidemiological basis for this possibility. Many laboratory experiments conducted in cell culture systems and in animal models have shown the usefulness of green tea, and the polyphenols present therein, against PCA. The epidemiological basis for this possibility is twofold. First, some epidemiological observations have suggested that people who consume tea regularly have a lower risk of PCA-related deaths. Second, the incidence of PCA in China, a population that consumes green tea on a regular basis, is lowest in the world.

29. Hakim IA, Harris RB, Weisgerber UM. Tea intake and squamous cell carcinoma of the skin: influence of type of tea beverages. *Cancer Epidemiol Biomarkers Prev.* 2000 Jul;9(7):727-31. Cancer Prevention and Control, Arizona Cancer Center, College of Medicine, University of Arizona, Tucson 85724, USA. ihakim@azcc.arizona.edu

Differences in tea drinking habits are likely to vary by populations and could contribute to the inconsistencies found between studies comparing tea consumption and cancer risk. A population-based case-control study was used to evaluate how usual tea consumption patterns of an older population ($n = 450$) varied with history of squamous cell carcinoma (SCC) of the skin. A

detailed tea questionnaire was developed to assess specific tea preparation methods and patterns of drinking. In this southwestern United States population, black tea was the predominant variety of tea consumed. We found no association between the broad definition of any tea consumption and skin SCC. However, the adjusted odds ratios (ORs) for hot and iced black tea intake were 0.63 [95% confidence interval (CI), 0.36-1.10] and 1.02 (95% CI, 0.64-1.63), respectively. Controls were more likely to report usually drinking strong hot tea (OR, 0.74; 95% CI, 0.53-1.03) with increased brewing time (P for trend = 0.03). Adjusting for brewing time, the association between skin SCC and hot black tea consumption suggests a significantly lower risk in consumers of hot tea compared to nonconsumers (OR, 0.33; 95% CI, 0.12-0.87). This is one of the first studies to explore the relation between different types of tea consumption and occurrence of human cancers. Our results show that tea concentration (strength), brewing time, and beverage temperature have major influences on the potential protective effects of hot black tea in relation to skin SCC. Further studies with increased sample sizes are needed to evaluate the interrelationships between preparation techniques, tea type, and other life-style factors.

30. Hankin JH, Nomura A, Rhoads GG. Dietary patterns among men of Japanese ancestry in Hawaii. *Cancer Res.* 1975 Nov;35(11 Pt. 2):3259-64.

The dietary patterns of 6663 men of Japanese ancestry, living in Hawaii and participating in the Honolulu Heart and Japan-Hawaii Cancer Studies, were analyzed according to country of birth and boyhood education. Approximately 80% of the men were born and educated in Hawaii (Nisei); the others were either born in Japan (Issei) or traveled to Japan for 5 or more years of boyhood education (Kibei). Twenty-four-hr diet recalls, obtained at the first cycle of examinations (1965 to 1968), revealed that the Nisei consumed significantly greater intakes of total and animal protein, total and saturated fat, and cholesterol than the Issei and Kibei. Values for weight, height, skinfold thickness, and serum cholesterol were in the same direction, and the differences were statistically significant. Food frequency questionnaires at the 1st and 3rd examinations covered a 6-year interval. At both time periods, the Issei and Kibei ate Japanese foods more frequently and in greater quantities than the Nisei. In general, the Nisei consumed more Western foods. Both food frequency questionnaires included 6 identical items; coffee, milk, green tea, rice, tofu (soybean curd), and tsukudani (preserved seaweed paste). The frequent and infrequent consumers were similarly characterized over the 6-year period. The findings suggest that the country of birth and education has lasting effects on adult eating patterns. The observed heterogeneity for specific food items and nutrients between the Nisei and Issei-Kibei men augers well for attempts to relate such items to chronic diseases such as cancer.

31. Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J, Adami HO. Diet and risk of gastric cancer. A population-based case-control study in Sweden. *Int J Cancer.* 1993 Sep 9;55(2):181-9.

A case-control study to evaluate risk factors of gastric cancer was carried out in areas with contrasting incidence rates in Sweden. Face-to-face interviews were conducted with 338 of 456 eligible histologically confirmed gastric-cancer cases and 669 of 880 eligible control subjects, sampled from population registers and frequency-matched by age and gender. We focused on 2 periods, adolescence and 20 years prior to interview. The association of gastric-cancer risk with

dietary habits during adolescence were similar to that found for the period 20 years before interview; high consumption of wholemeal bread, fruit and vegetables was associated with reduced gastric-cancer risk. In addition, cheese, fish and tea had a protective effect during adolescence. Increased gastric-cancer risk was related to whole-milk consumption, but this association decreased substantially in a multivariate analysis including vegetables. There was a positive relationship between gastric-cancer risk and the age at which the interviewees started using refrigerators. This population-based study confirmed the protective effect of a high consumption of vegetables and fruit in the development of gastric cancer, but failed to find any association between intake of meat, sausage, cold cuts, liver, salt, coffee, the habit of frying, smoking or grilling foods, and risk of gastric cancer.

32. Hara N, Sakata K, Nagai M, Fujita Y, Hashimoto T, Yanagawa H. Statistical analyses on the pattern of food consumption and digestive-tract cancers in Japan. *Nutr Cancer*. 1985;6(4):220-8.

The relationships between areal differences in mortality from six digestive-tract cancers and consumption of selected foods in 46 of the 47 Japanese prefectures (Okinawa being excluded) were analyzed. Statistical analyses disclosed that the groups of foods positively associated with cancer death were as follows: for esophageal cancer, pork, oil, popular-grade sake, and green tea; for stomach cancer, fresh fish, salted or dried fish, salt, and special-grade sake; for colon cancer, bread, milk, butter, margarine, ketchup, beer, and salted or dried fish; for rectal cancer, fresh fish, salted or dried fish, salt, and popular-grade sake; for cancer of the biliary passages, pork, popular-grade sake, and green tea; and for pancreatic cancer, oil, mayonnaise, fresh fish, and salted or dried fish. These results are based on statistical analyses. Further epidemiological analyses are required to find a biological causal relationship.

33. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*. 1997 Dec;6(12):1081-6.

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To assess the relationship of smoking and coffee, tea, and alcohol intake to the risk of cancer of the exocrine pancreas, analyses were performed using data from a prospective cohort study of 33,976 postmenopausal Iowa women who responded to a mailed questionnaire in 1986 and were followed through 1994 for cancer incidence and total mortality. At baseline, information on cigarette smoking, consumption of tea, coffee, and alcoholic beverages, and other dietary and lifestyle factors was obtained. Age-adjusted relative risks of pancreatic cancer ($n = 66$ cases) showed a dose-response association with smoking. Those with fewer than 20 pack-years and those with 20 or more pack-years of smoking exposure were 1.14 (95% confidence interval, 0.53-2.45) and 1.92 (95% confidence interval, 1.12-2.30) times more likely, respectively, to develop pancreatic cancer than were nonsmokers. Current smokers were twice as likely as were nonsmokers to develop pancreatic cancer. Relative risks of pancreatic cancer increased with the

amount of alcohol consumed ($P_{\text{trend}} = 0.11$) after adjustment for age, smoking status, and pack-years of smoking. Relative risks of pancreatic cancer according to alcoholic beverage intake were as strong among never-smokers as they were in the total cohort. After the data were adjusted for age, smoking status, and pack-years of smoking, there was a statistically significant 2-fold (95% confidence interval, 1.08-4.30) elevated risk of pancreatic cancer for those who drank > 17.5 cups of coffee per week, compared to those who consumed < 7 cups/week; among never-smokers, the relative risks across coffee intake categories were still positive but were attenuated somewhat ($P_{\text{trend}} = 0.17$). Tea intake was not related to cancer incidence. In summary, these findings provide evidence of an association of both alcoholic beverage and coffee consumption with pancreatic cancer incidence that is independent of age and cigarette smoking.

34. Hartge P, Hoover R, West DW, Lyon JL. Coffee drinking and risk of bladder cancer. *J Natl Cancer Inst.* 1983 Jun;70(6):1021-6.

The relationship between coffee drinking and risk of bladder cancer was assessed with the use of data from a case-control study of bladder cancer. Incident cases (2,982) and general population controls (5,782) were interviewed. Overall, the relative risk (RR) of bladder cancer for subjects who had ever drunk coffee was estimated as 1.4 (95% confidence interval = 1.1-1.8). There was no consistent relation between the RR estimate and the current consumption level. Among men who drank coffee, those who drank more than 49 cupfuls of coffee per week had an apparent excess in risk, but women who drank that much had an apparent deficit in risk. Howe GR, Burch JD, Miller AB, et al. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *Natl Cancer Inst.* 1980 Apr;64(4):701-13.

35. Hartman TJ, Tangrea JA, Pietinen P, Malila N, Virtanen M, Taylor PR, Albanes D. Tea and coffee consumption and risk of colon and rectal cancer in middle-aged Finnish men. *Nutr Cancer.* 1998;31(1):41-8.

The association between coffee and black tea consumption and the subsequent risk of colon and rectal cancer was investigated within a Finnish clinical trial cohort. One hundred eleven cases of colon cancer and 83 cases of rectal cancer were diagnosed over a median of 9.0 years of follow-up. Proportional hazards regression models were used to derive adjusted relative risk (RR) and 95% confidence intervals (CI) for the association between coffee and tea consumption and cancer incidence. After controlling for confounders, coffee was not significantly associated with colon or rectal cancer. A positive association was seen for increased consumption of tea drinking and colon cancer. Compared with persons who did not drink tea, those who consumed <1 cup/day had an RR of 1.40 (95% CI = 0.84 - 2.33) and those who consumed > or = 1 cup/day had an RR of 2.09 (95% CI = 1.34-3.26, p for trend = 0.001). In contrast, tea consumption had little effect on rectal cancer incidence. This study does not support the hypothesis that coffee and tea protect against colorectal cancer risk. However, given the strength of the tea-colon cancer association and the significant gradient of risk we observed across level of intake, further epidemiologic research of this relationship in other populations seems warranted.

36. Heilbrun LK, Nomura A, Stemmermann GN. Black tea consumption and cancer risk: a prospective study. *Br J Cancer*. 1986 Oct;54(4):677-83.

In a prospective cohort study, men of Japanese ancestry were clinically examined from 1965 to 1968. For 7,833 of these men, data on black tea consumption habits were recorded. Since 1965, newly diagnosed cancer incidence cases have been identified: 152 colon, 151 lung, 149 prostate, 136 stomach, 76 rectum, 57 bladder, 30 pancreas, 25 liver, 12 kidney and 163 at other (miscellaneous) sites. Compared to almost-never drinkers, men habitually drinking black tea more than once/day had an increased relative risk (RR) for rectal cancer (RR = 4.2). This positive association ($P = 0.0007$) could not be accounted for by age or alcohol intake. We also observed a weaker but significant negative association of black tea intake and prostate cancer incidence ($P = 0.020$). There were no significant associations between black tea consumption and cancer at any other site.

37. Hiatt RA, Klatsky AL, Armstrong MA. Pancreatic cancer, blood glucose and beverage consumption. *Int J Cancer*. 1988 Jun 15;41(6):794-7.

Division of Research, Kaiser Permanente Medical Center, Oakland, CA 94611.

We studied the incidence of pancreatic cancer in 122,894 men and women who had previously reported amount and frequency of coffee, tea, and alcohol consumption; reporting was done at a multi-phasic health check-up (MHC) taken while subjects were members of a large prepaid health plan. We also tested the hypothesis that a pre-clinical effect of pancreatic cancer on glucose homeostasis leads to mild hyperglycemia and a generally increased thirst. If true, this could partially explain the increased consumption of beverages (particularly coffee) reported in association with pancreatic cancer in some case-control studies. However, in the 49 pancreatic cancer cases diagnosed during 6 years of follow-up, we found no evidence of increased risk associated with coffee, tea, or alcoholic beverages. We also found no evidence to support the increased-thirst hypothesis when we examined the 19 cases diagnosed within 12 months of having MHC. We did confirm a significantly increased risk among cigarette smokers (relative risk, 2.5; 95% confidence interval, 1.3-4.7) which was progressive with increasing levels of cigarette use. In addition, risk of pancreatic cancer was greater for persons previously under treatment for diabetes mellitus (relative risk, 4.5; 95% confidence interval, 1.2-16.7). Our results add to the growing body of evidence against a causal role of coffee in pancreatic cancer.

38. Higginson J. Etiological factors in gastrointestinal cancer in man. *J Natl Cancer Inst*. 1966 Oct;37(4):527-45.

No significant association was found between stomach cancer risk and tea consumption

39. Hoshiyama Y, Kawaguchi T, Miura Y, Mizoue T, Tokui N, Yatsuya H, Sakata K, Kondo T, Kikuchi S, Toyoshima H, Hayakawa N, Tamakoshi A, Ohno Y, Yoshimura T; Japan Collaborative Cohort Study Group. A prospective study of stomach cancer death in relation to green tea consumption in Japan. *Br J Cancer* 2002;87:309-13.

To evaluate whether green tea consumption provides protection against stomach cancer death, relative risks were calculated using Cox proportional hazards regression analysis in the Japan Collaborative Study for Evaluation of Cancer Risk, sponsored by the Ministry of Health and Welfare (JACC Study). The study was based on 30 370 men and 42 481 women aged 40-79. After adjustment for age, smoking status, history of peptic ulcer, family history of stomach cancer along with certain dietary items, the risks associated with drinking one or two, three or four, five to nine, and 10 or more cups of green tea per day, relative to those of drinking less than one cup per day, were 1.6 (95% CI: 0.9-2.9), 1.1 (95% CI: 0.6-1.9), 1.0 (95% CI: 0.5-2.0), and 1.0 (95% CI: 0.5-2.0), respectively, in men (P for trend=0.669), and 1.1 (95% CI: 0.5-2.5), 1.0 (95% CI: 0.5-2.5), 0.8 (95% CI: 0.4-1.6), and 0.8 (95% CI: 0.3-2.1), respectively, in women (P for trend=0.488). The authors found no inverse association between green tea consumption and the risk of stomach cancer death.

40. Hoshiyama Y, Sasaba T. A case-control study of stomach cancer and its relation to diet, cigarettes, and alcohol consumption in Saitama Prefecture, Japan. *Cancer Causes Control*. 1992 Sep;3(5):441-8.

A case-control study of stomach cancer in relation to dietary, smoking, and drinking habits was undertaken in Saitama Prefecture, Japan. The study was based on 294 cases of newly diagnosed adenocarcinoma of the stomach at a single institution, 294 general population controls (matched by sex, age, and administrative division), and 202 hospital controls. Dietary habits were investigated based on the intake of 12 separate foods and 12 food groups in a food frequency questionnaire, together with individual food preferences. The consumption of raw vegetables was inversely related to the risk of stomach cancer, with a dose-response relation observed consistently in the comparisons with both sets of controls. Current cigarette smokers (1-29/day) had an increased risk (relative risk = 1.8, 95 percent confidence interval = 1.1-3.0) compared with nonsmokers in the general population controls, but no dose-response effect with heavier cigarette smoking. Alcohol use did not affect the risk of stomach cancer. In the multiple logistic regression, the consumption of raw vegetables showed a protective effect on stomach cancer while cigarette smoking had no significant association, in both sets of controls.

41. Howe GR, Burch JD, Miller AB, et al. Tobacco use, occupation, coffee, various nutrients, and bladder cancer. *Natl Cancer Inst*. 1980 Apr;64(4):701-13.

In a Canadian population-based case-control study of 480 males and 152 female case-control pairs, the relative risk for development of bladder cancer for ever used versus never used cigarettes was 3.9 for males and 2.4 for females, with a dose-response relationship in both sexes. A reduced risk was associated with the use of filter cigarettes compared to nonfilter cigarettes. After control for cigarette usage, a significant risk was noted for male pipe smokers. For male ex-smokers the risk after 15 years of no smoking was less than one-half that of current male smokers. Bladder cancer risk was found for workers in the chemical, rubber, photographic, petroleum, medical, and food processing industries among males and for workers occupationally exposed to dust or fumes among both sexes. Bladder cancer risk was elevated for males consuming all types of coffee, regular coffee, and instant coffee and for females consuming

instant coffee, but no dose-response relationship was found. Risk was found for males consuming water from nonpublic supplies but not for females. No risk was observed in males or females consuming nitrate-containing foods, beverages other than coffee, or fiddlehead greens. Hair dye usage in females and phenacetin usage in males and females carried no risk. Divergent findings by area for aspirin suggested that an overall association was not causal. Reevaluation of the data on artificial sweeteners confirmed a significant bladder cancer risk in males and a dose-response relationship. The cumulated population attributable risk for bladder cancer was 90% for males from cigarette smoking, industrial exposure, and exposure to nonpublic water supplies and 29% for females from cigarette smoking, industrial exposure, and instant coffee consumption.

42. Hu J, Nyren O, Wolk A, Bergstrom R, Yuen J, Adami HO, Guo L, Li H, Huang G, Xu X, et al. Risk factors for oesophageal cancer in northeast China. *Int J Cancer*. 1994 Apr 1;57(1):38-46.

A hospital-based case-control study of oesophageal cancer was carried out in the Heilongjiang Province, a low-risk area for oesophageal cancer in China. From May 1985 to May 1989, 196 histologically confirmed cases and 392 controls with other (non-neoplastic) diseases were personally interviewed in the wards of 5 major hospitals. Information was obtained about usual consumption in the early 1980s of 32 major contributors to the diet in the province, socio-demographic status, smoking and alcohol consumption. Odds ratios (OR) were obtained from logistic regression models, and confounding was controlled by means of multivariate models. Smoking and alcohol consumption were major risk factors for oesophageal cancer in this population. Smokers of handmade cigarettes exhibited a particularly high risk. A near multiplicative synergism was found between smoking and alcohol consumption. There was a significant inverse dose-risk trend for combined consumption of vegetables and fruits; a 300-g increase per day lowered risk by 35%. Vitamin C intake was negatively associated with risk; a 100-mg increase per day lowered risk by 39%. Our data suggest a modifying effect of vitamin C and beta-carotene on risk associated with smoking, but the power of analyses was low. Salt, salt-preserved foods and pickled vegetables were not associated with increased risk. High temperature of meals and drinks was a strong risk indicator in this population. The strength of tea and overall tea consumption were independent determinants of the risk.

43. Huang C, Zhang X, Qiao Z, Guan L, Peng S, Liu J, Xie R, Zheng L. A case-control study of dietary factors in patients with lung cancer. *Biomed Environ Sci*. 1992 Sep;5(3):257-65.

School of Public Health, West China University of Medical Sciences (WCUMS), Chengdu.

A case-control study was designed to investigate association of dietary factors with the risk of lung cancer in Sichuan, China. The cases consisted of 135 patients with preinvasive lung cancer which had been confirmed with histopathology, fiber bronchoscope, CT and X-ray film in three provincial hospitals in the recent one year. Controls were healthy subjects who went to one of these hospitals for health check-up; patients with pulmonary diseases was excluded. Controls were matched to cases for sex and age with a ratio of 1:1. Nutrient intakes, the eating habit and other relevant factors were investigated. The data analyzed with the conditional logistic regression model indicated that dietary beta-carotene intakes had a significantly inverse association with the risk of lung cancer. Vitamin C had a less significantly inverse association

with the risk. Association of protein, fat, energy, retinol intakes or diet-balance index with the risk was not significant. Association of tea, alcohol, garlic or mushroom, respectively, with the risk was also not observed. Consumption of more processed foods and deep-fried foods were found to be risk factors. Smoking and air pollution from coal burning stoves were also observed as independent risk factors of lung cancer in the present study. The mental stress incidence in the case was significantly higher than that in the control.

44. Imai K, Suga K, Nakachi K. Cancer-preventive effects of drinking green tea among a Japanese population. *Prev Med* 1997 Nov-Dec;26(6):769-775.

BACKGROUND: Laboratory studies have revealed the cancer preventive effects of green tea, so the association between green tea consumption and cancer was examined in a human population. **METHODS:** The association between green tea consumption and cancer incidence was studied in our prospective cohort study of a Japanese population. We surveyed 8,552 individuals over 40 years of age living in a town in Saitama prefecture on their living habits, including daily consumption of green tea. During the 9 years of follow-up study (71,248.5 person-years), we identified a total of 384 cases of cancer in all sites. **RESULTS:** We found a negative association between green tea consumption and cancer incidence, especially among females drinking more than 10 cups a day. The slowdown in increase of cancer incidence with age observed among females who consumed more than 10 cups a day is consistent with the finding that increased consumption of green tea is associated with later onset of cancer. Age-standardized average annual incidence rate was significantly lower among females who consumed large amounts of green tea. Relative risk (RR) of cancer incidence was also lower among both females (RR = 0.57, 95% CI = 0.33-0.98) and males (RR = 0.68, 95% CI = 0.39-1.21) in groups with the highest consumption, although the preventive effects did not achieve statistical significance among males, even when stratified by smoking and adjusted for alcohol and dietary variables. **CONCLUSION:** Our epidemiological study showed that green tea has a potentially preventive effect against cancer among humans.

45. Inoue M, Tajima K, Hirose K, Hamajima N, Takezaki T, Kuroishi T, Tominaga S. Tea and coffee consumption and the risk of digestive tract cancers: data from a comparative case-referent study in Japan. *Cancer Causes Control*. 1998 Mar;9(2):209-16.
Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya, Japan.

OBJECTIVES: The purpose of this study was to examine the hypothesis that tea and coffee consumption have a protective effect against development of digestive tract cancers. **METHODS:** A comparative case-referent study was conducted using Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) data from 1990 to 1995 in Nagoya, Japan. This study comprised 1,706 histologically diagnosed cases of digestive tract cancers (185 esophagus, 893 stomach, 362 colon, 266 rectum) and a total of 21,128 non-cancer outpatients aged 40 years and over. Logistic regression was used to analyze the data, adjusting for gender; age; year and season at hospital-visit; habitual smoking and alcohol drinking; regular physical exercise; fruit, rice, and beef intake; and beverage intake. **RESULTS:** The odds ratio (OR) of stomach cancer decreased to 0.69 (95 percent confidence interval [CI] = 0.48-1.00) with high intake of green tea (seven cups or more per day). A decreased risk was also observed for rectal cancer with three cups or more daily intake of coffee (OR = 0.46, CI = 0.26-0.81).

CONCLUSIONS: The results suggest the potential for protective effect against site-specific digestive tract cancer by consumption of green tea and coffee, although most associations are limited only to the upper category of intake and have no clear explanation for site-specificity.

46. Inoue M, Tajima K, Hirose K, Kuroishi T, Gao CM, Kitoh T. Life-style and subsite of gastric cancer--joint effect of smoking and drinking habits. *Int J Cancer*. 1994 Feb 15;56(4):494-9.

Division of Epidemiology, Aichi Cancer Center Research Institute, Nagoya, Japan. To clarify the effects of life-style on gastric cancer by subsite focusing on the proximal part (cardia and fundus) and the distal part (pyloric antrum), a case-control study was conducted at the Aichi Cancer Center in Nagoya, Japan from 1988-1991. This study compared 668 histologically confirmed gastric cancer cases [123 cardia, 218 middle (body), 256 antrum, and 71 unclassified] with 668 controls using a common questionnaire about life-styles as related to smoking, drinking, dietary habits and frequency of food intake. Controls were selected from among outpatients of the same hospital. Controls free of cancer and other specific diseases were matched with cases for sex, age (within 2 years), and time of hospital visit (within 2 months). A Western-style breakfast decreased the risk of antrum cancer, while consumption of greasy food increased the risk of cardia cancer. Fresh vegetables decreased the risk of cancer in both cardia and antrum. Habitual smoking is associated with increased risk of gastric cancer and it is more prominent in cardia cancer, especially in those who are drinkers. Results obtained from this study suggest that risk factors and relative risks of gastric cancer varied by subsite to a considerable degree. Furthermore, the joint effect of smoking and drinking may play an important role in the development of gastric cancer, especially of cardia cancer.

47. Inoue M, Tajima K, Mizutani M, Iwata H, Iwase T, Miura S, Hirose K, Hamajima N, Tominaga S. Regular consumption of green tea and the risk of breast cancer recurrence: follow-up study from the Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC), Japan. *Cancer Lett* 2001;167:175-82.

Division of Epidemiology and Prevention, Aichi Cancer Center Research Institute, 1-1 Kanokoden, Chikusa-ku, Nagoya 464-8681, Japan.

This study was conducted to examine the association between regular green tea consumption prior to diagnosis and subsequent risk of breast cancer recurrence. The Hospital-based Epidemiologic Research Program at Aichi Cancer Center (HERPACC) was started in 1988, in which information on lifestyle has routinely been collected from all first-visit outpatients by questionnaire. A total of 1160 new surgical cases of female invasive breast cancers with HERPACC information diagnosed between June 1990 and August 1998 were followed up through December 1999, and the risk (hazard ratio: HR) of recurrence was assessed with reference to daily green tea consumption using a Cox proportional hazard model. During 5264 person-years of follow-up, 133 subjects (12%) were documented to suffer recurrence of breast cancer. A decreased HR for recurrence adjusted for stage was observed with consumption of three or more daily cups of green tea (HR=0.69, 95% confidence interval (95%CI)=0.47-1.00). Particularly in stage I, the HR was decreased statistically significantly (HR=0.43, 95%CI=0.22-0.84). A similar tendency was observed for stage II subjects, but was not present among more advanced stages. Although careful interpretation is needed, these results suggest the possibility

that regular green tea consumption may be preventive against recurrence of breast cancer in early stage cases.

48. Iscovich J, Castelletto R, Esteve J, Munoz N, Colanzi R, Coronel A, Deamezola I, Tassi V, Arslan A. Tobacco smoking, occupational exposure and bladder cancer in Argentina. *Int J Cancer*. 1987 Dec 15;40(6):734-40.

The highest rate for bladder cancer in Latin America has been reported from La Plata, Argentina. A case-control study was carried out to investigate the reasons for this high rate. A total of 117 cases, 117 hospital controls and 117 neighbourhood sex- and age-matched controls were interviewed regarding their smoking and drinking habits and occupational exposures. Cigarette smoking and coffee drinking were identified as the major risk factors, and a significant association was also found for truck and railway drivers and for oil refinery workers. The relative risks for male smokers who ever smoked cigarettes vs. non-smokers was 4.3 (95% CI: 1.9-10.3). The risk associated with black tobacco cigarettes was 2-3 times higher than that of blond cigarettes. For male ex-smokers the risk after 5 years of no smoking is less than one third of that of current smokers. The RR for drinking coffee was 2.4 (95% CI: 1.4-4.4) after adjusting for the effects of tobacco smoking, and the risk increased with the number of cups per day. No association was found with the use of saccharin and tea drinking.

49. Jain M, Howe GR, St Louis P, Miller AB. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer*. 1991 Feb 1;47(3):384-9.

Results are reported from a population-based study of 249 cases of pancreas cancer and 505 controls carried out in Toronto, Canada, between 1983 and 1986. Lifetime consumption of coffee and alcohol and medical histories was assessed by personal interviews. No evidence of any association was found with different types of coffee, tea or alcohol after adjusting for smoking, calories and fibre intake. There was a significant increased risk associated with a history of diabetes mellitus within 5 years of cancer development. A protective effect of a history of some allergic conditions, hay fever, eczema and asthma, was observed, although the relative risks were not significant (p value greater than 0.10).

50. Jain MG, Hislop GT, Howe GR, Burch JD, Ghadirian P. Alcohol and other beverage use and prostate cancer risk among Canadian men. *Int J Cancer*. 1998 Dec 9;78(6):707-11.
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There are very few large scale studies that have examined the association of prostate cancer with alcohol and other beverages. This relationship was examined in a case-control study conducted in 3 geographical areas of Canada [Metropolitan Toronto (Ontario), Montreal (Quebec), and Vancouver (British Columbia)] with 617 incident cases and 637 population controls. Complete history of beverage intake was assessed by a personal interview with reference to a 1-year period prior to diagnosis or interview. In age- and energy-adjusted models for all centers combined, the odds ratio (OR) for the highest quintile of total alcohol intake was 0.89. For alcoholic beverages separately, it was 0.68 for the highest tertile of beer, 1.12 for wine and 0.86 for liquor. The

decreasing trend was significant for beer intake. The results were only significant for British Columbia out of all the 3 centers studied. Whereas coffee and cola intake was not associated with prostate cancer, a decrease in risk was observed with tea intake of more than 500 g per day (OR 0.70). Our results do not support a positive association between total alcohol, coffee and prostate cancer.

51. Jensen OM, Wahrendorf J, Knudsen JB, Sorensen BL. The Copenhagen case-control study of bladder cancer. II. Effect of coffee and other beverages. *Int J Cancer*. 1986 May 15;37(5):651-7.

During the years 1979-1981 a population-based case-control study of bladder cancer including papilloma was performed in greater Copenhagen. A total of 371 patients (280 males; 91 females), and a comparable age- and sex-stratified group of 771 controls (577 males; 194 females) remained for logistic regression analysis. Controls were selected at random from the general population of the study area. All persons were questioned about their drinking habits with respect to coffee, tea and other beverages, as well as their exposure to a number of known or suspected risk factors for bladder cancer. After adjustment for tobacco smoking, the relative risk of bladder cancer in relation to coffee drinking was not statistically significant among either men or women. A significant association was found between bladder cancer and tea drinking among men, but with no regular trend for increasing consumption. An association was found between risk of bladder cancer and both total daily liquid intake and non-cola soft drinks. This population-based case-control study provides no evidence of an isolated influence of coffee drinking, tea drinking or caffeine intake on bladder cancer risk.

52. Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, Blot WJ, Fraumeni JF Jr. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer* 1997 Jan 27;70(3):255-8.

The effect of green tea drinking in reducing human cancer risk is unclear, though a protective effect has been reported in numerous animal studies and several epidemiologic investigations. Herein the hypothesis that green tea consumption may reduce the risk of cancers of the colon, rectum and pancreas is examined in a large population-based case-control study conducted in Shanghai, China. Newly diagnosed cancer cases (931 colon, 884 rectum and 451 pancreas) during 1990-1993 among residents 30-74 years of age were included. Controls (n = 1,552) were selected among Shanghai residents and frequency-matched to cases by gender and age. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) of each cancer associated with green tea consumption were derived after adjustment for age, income, education and cigarette smoking. Additional adjustment for dietary items and body size was found to have minimal impact. An inverse association with each cancer was observed with increasing amount of green tea consumption, with the strongest trends for rectal and pancreatic cancers. For men, compared with non-regular tea drinkers, ORs among those in the highest tea consumption category (≥ 300 g/month) were 0.82 for colon cancer, 0.72 for rectal cancer and 0.63 for pancreatic cancer, with p values for trend being 0.38, 0.04 and 0.04, respectively. For women, the respective ORs for the highest consumption category (≥ 200 g/month) were 0.67, 0.57 and 0.53, with the respective p values for trend being 0.07, 0.001 and 0.008. Our findings

provide further evidence that green tea drinking may lower the risk of colorectal and pancreatic cancers.

53. Ji BT, Chow WH, Yang G, McLaughlin JK, Gao RN, Zheng W, Shu XO, Jin F, Fraumeni JF Jr, Gao YT. The influence of cigarette smoking, alcohol, and green tea consumption on the risk of carcinoma of the cardia and distal stomach in Shanghai, China. *Cancer*. 1996 Jun 15;77(12):2449-57.

BACKGROUND: The divergent incidence patterns of gastric cardia and distal stomach cancer may suggest different etiologies. This study examined the role of cigarette smoking, alcohol drinking, and green tea consumption as risk factors for carcinoma by anatomic subsite of stomach. **METHODS:** Newly-diagnosed stomach carcinoma patients (n = 1124) and frequency-matched population controls (n = 1451) were interviewed in person. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression models. **RESULTS:** Excess risks associated with cigarette smoking and alcohol consumption were observed largely among men. The adjusted ORs for all stomach cancer combined were 1.35 (CI: 1.06-1.71) for current smokers, and 1.26 (CI: 0.86-1.84) for ex-smokers. For tumors of the distal stomach, statistically significant positive dose-response trends were found for the number of cigarettes smoked per day, the duration and pack-years of smoking, and inverse trends for years of stopped smoking. For tumors of the gastric cardia, however, a monotonic association was found only for the number of cigarettes smoked per day (P=0.06). Alcohol consumption was not related to the risk of cardia cancer, while a moderate excess risk of distal stomach cancer (OR: 1.55; CI: 1.07-2.26) was observed among heavy alcohol drinkers. Green tea drinking was inversely associated with risk of stomach cancer arising from either subsite, with ORs of 0.77 (CI: 0.52-1.13) among female heavy drinkers, and 0.76 (CI: 0.55-1.27) among male heavy drinkers. **CONCLUSIONS:** Our findings provide further evidence that cigarette smoking and, possibly, alcohol consumption increase the risk of stomach carcinoma, notably of the distal segment. An inverse association with green tea drinking was also observed.

54. Kamat AM, Lamm DL. Chemoprevention of bladder cancer. *Urol Clin North Am* 2002 ;29:157-68.

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Among the numerous other compounds and dietary substances purported to have chemopreventive effect, soybeans, garlic, and green tea stand out as having the greatest promise and can freely be recommended to patients. There is a mistaken notion that simply because an agent is naturally occurring, it cannot be as beneficial as taking a substance synthesized in the laboratory. Encouraging patients to follow an essentially healthy food habit lifestyle will be a significant contribution in the fight against cancer.

55. Kato I, Tominaga S, Matsuura A, Yoshii Y, Shirai M, Kobayashi S. A comparative case-control study of colorectal cancer and adenoma. *Jpn J Cancer Res.* 1990;81(11):1101-8.

We conducted a comparative case-control study of colorectal cancer and adenoma involving 221 cases with colorectal cancer, 525 cases with colorectal adenoma and 578 neighborhood controls. Daily vegetables intake was associated with lower risks of distal colon adenoma (relative risks (RR) = 0.59, 95% confidence interval (CI): 0.39-0.89) and rectal cancer (RR = 0.46, 95% CI: 0.25-0.84). Daily beans intake was associated with lower risk of colon adenoma (RR = 0.58, 95% CI: 0.37-0.91 for the proximal colon and RR = 0.63, 95% CI: 0.45-0.88 for the distal colon) and daily intake of seaweeds was associated with lower risk of rectal cancer (RR = 0.42, 95% CI: 0.22-0.82). Daily intake of fish and shellfish also showed an inverse association with the risk of colon adenoma (RR = 0.67, 95% CI: 0.45-0.99 for the proximal colon and RR = 0.70, 0.52-0.94 for the distal colon). Generally, intakes of animal or vegetable fat-rich foods, especially meats, were associated with decreases in risks of both adenoma and cancer, though the association of cancer was not statistically significant. Other than dietary factors, daily alcohol drinking was associated with an increased risk of adenoma in the proximal colon (RR = 1.95, 95% CI: 1.15-3.29) and ex-drinkers showed higher risks for colon adenoma and colorectal cancer. Sports or occupational activities and coffee drinking were inversely associated and family history of colorectal cancer was positively associated with the risk of both colorectal adenoma and cancer. Daily intake of hot green tea was inversely associated with the risks of distal colon and rectal adenomas and colon cancer (page 1103).

56. Kinjo Y, Cui Y, Akiba S, Watanabe S, Yamaguchi N, Sobue T, Mizuno S, Beral V. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. *J Epidemiol.* 1998 Oct;8(4):235-43.

To clarify mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet, further analyses on the data from a large prospective cohort study in Japan were conducted. The subjects for analysis were 220,272 men and women aged 40 to 69 at the baseline of 1965. There were 440 oesophageal cancer deaths during the period from January 1966 to December 1981. Person-years at risk were 3,065,182 in total. Rate ratio and 95% confidence interval adjusted for attained age, prefecture, occupation and sex were (RR (95% CI)): 1.6 (1.2-2.0) for hot tea (drinking green tea at high temperatures) in comparison with not-hot tea (drinking green tea at moderate temperatures); 2.4 (1.8-3.1) for daily (4 times/week or more) alcohol drinking in comparison with non-drinking; and 2.3 (1.7-3.1) for heavy smoking (15 cigarettes/day or more) in comparison with non-smoking. Dose-response relationships were found in alcohol drinking and smoking among men and women (p for trend; $p < 0.001$). The rate ratios were not significantly associated with the dietary factors except for green-yellow vegetables (1-3 times/month or less in comparison with daily; RR = 2.0, 95% CI: 1.2-3.1), where a no dose-response trend was observed ($p = 0.45$). In comparison based on the binary variables, the RR for the subjects with daily alcohol drinking and current smoking was 3.9 with 95% CI of 2.7 to 5.4, relative to those exposed to neither habit. The joint effect of alcohol drinking (A) and smoking (S) was more than additive ($A*S > A + S$: $3.9 > 1 + (1.0-1) + (1.6-1)$). Further sub-analysis showed that the RR for the subjects with daily alcohol drinking, current smoking and hot tea was 5.7 with 95% CI of 3.7 to 8.9, when the reference was the subjects with not-daily alcohol

drinking, non-smoking and not-hot tea. Similar results were obtained from further adjustment of green-yellow vegetables. It is concluded that mortality risks of oesophageal cancer in the present cohort were substantially associated with thermal effect of hot tea, alcohol drinking, smoking and lower consumption of green-yellow vegetables. This finding suggests that life-style modification for smoking and dietary habits is essential to reduce the risks of oesophageal cancer in Japan.

57. Kinlen LJ, Willows AN, Goldblatt P, Yudkin J. Tea consumption and cancer. *Br J Cancer*. 1988 Sep;58(3):397-401.

Following the report from Hawaii (Heilbrun et al., 1986) of relationships between tea consumption and respectively rectal cancer (positive) and prostate cancer (negative), these questions were examined using data from a prospective mortality study of London men initiated in 1967. The small numbers of men who did not usually drink any tea prevented a reliable study of this sub group. Nevertheless no evidence of a dose-response relationship was found for rectal, colon or prostate cancer. Significant relationships were found, however, between tea consumption and deaths from stomach, lung and kidney cancers. In the case of stomach and lung cancer, these were partly due to the effects of social class and smoking, and possible reasons are considered for the residual relations.

58. Klatsky AL, Armstrong MA, Friedman GD. Coffee, tea, and mortality. *Ann Epidemiol*. 1993 Jul;3(4):375-81.

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Except for conflicting evidence about coffee and risk of coronary disease, coffee and tea are not linked to major causes of death. Because of widespread use of both beverages and limitations of prior studies, concern persists. Using Cox models (ten covariates) we studied relations in 128,934 persons to 4501 subsequent deaths. Except for slightly increased risk from acute myocardial infarction among heavier (≥ 4 cups/d) coffee users (relative risk versus nondrinkers = 1.4, 95% confidence interval = 1.0 to 1.9, $P = 0.07$), there was no increased risk of mortality for all deaths (relative risk per cup of coffee per day = 0.99, 95% confidence interval = 0.97 to 1.01; relative risk per cup of tea per day = 0.98, 95% confidence interval = 0.96 to 1.00) or major causes in adjusted analyses. Coffee was related to lower risk of liver cirrhosis death (relative risk per cup of coffee per day = 0.77, 95% confidence interval = 0.67 to 0.89). Use of both beverages was related to a lower risk of suicide, progressively lower at higher coffee intake (relative risk per cup of coffee per day = 0.87, 95% confidence interval = 0.77 to 0.98). We conclude that coffee and tea have no overall relation to mortality risk. If coffee increases coronary risk, this is balanced by an unexplained lower risk of other conditions, notably cirrhosis and suicide.

59. Knekt P, Jarvinen R, Seppanen R, Heliovaara M, Teppo L, Pukkala E, Aromaa A. Dietary flavonoids and the risk of lung cancer and other malignant neoplasms. *Am J Epidemiol*. 1997 Aug 1;146(3):223-30.

National Public Health Institute, Helsinki, Finland.

Flavonoids are effective antioxidants and, in theory, may provide protection against cancer, although direct human evidence of this is scarce. The relation between the intake of antioxidant flavonoids and subsequent risk of cancer was studied among 9,959 Finnish men and women aged 15-99 years and initially cancer free. Food consumption was estimated by the dietary history method, covering the total habitual diet during the previous year. During a follow-up in 1967-1991, 997 cancer cases and 151 lung cancer cases were diagnosed. An inverse association was observed between the intake of flavonoids and incidence of all sites of cancer combined. The sex- and age-adjusted relative risk of all sites of cancer combined between the highest and lowest quartiles of flavonoid intake was 0.80 (95% confidence interval 0.67-0.96). This association was mainly a result of lung cancer, which presented a corresponding relative risk of 0.54 (95% confidence interval 0.34-0.87). The association between flavonoid intake and lung cancer incidence was not due to the intake of antioxidant vitamins or other potential confounding factors, as adjustment for factors such as smoking and intakes of energy, vitamin E, vitamin C, and beta-carotene did not materially alter the results. The association was strongest in persons under 50 years of age and in nonsmokers with relative risks of 0.33 (95% confidence interval 0.15-0.77) and 0.13 (95% confidence interval 0.03-0.58), respectively. Of the major dietary flavonoid sources, the consumption of apples showed an inverse association with lung cancer incidence, with a relative risk of 0.42 (95% confidence interval 0.23-0.76) after adjustment for the intake of other fruits and vegetables. The results are in line with the hypothesis that flavonoid intake in some circumstances may be involved in the cancer process, resulting in lowered risks.

60. Koizumi Y, Tsubono Y, Nakaya N, Nishino Y, Shibuya D, Matsuoka H, Tsuji I. No association between green tea and the risk of gastric cancer: pooled analysis of two prospective studies in Japan. *Cancer Epidemiol Biomarkers Prev*. 2003 May;12(5):472-3.
Division of Epidemiology, Department of Public Health and Forensic Medicine, Tohoku University Graduate School of Medicine, Sendai 980-8575, Japan.

No inverse relationship was found between consumption of green tea and risk of stomach cancer when analysis was performed by pooling two independent studies conducted among responding residents in different locations.

61. Kono S, Ikeda M, Tokudome S, Kuratsune M. A case-control study of gastric cancer and diet in northern Kyushu, Japan. *Jpn J Cancer Res*. 1988 Oct;79(10):1067-74.

A case-control study of gastric cancer was done in a rural area of northern Kyushu, Japan, in relation to dietary habits especially focusing on the relationship with the consumption of broiled fish. The study was based upon 139 cases of newly diagnosed gastric cancer at a single institution, 2,574 hospital controls and 278 controls sampled randomly from the residents of the study area (with sex and year of birth matched). No association was observed between the

consumption of broiled fish and gastric cancer risk whether three types of broiled fish (raw fish, dried fish and salted fish) were analyzed separately or as a single category. However, consistently in the comparisons with both sets of controls, the risk of gastric cancer was inversely related with the consumption of fruits and positively associated with cigarette smoking. A decreased risk of gastric cancer was also noted among those with high consumption of green tea (10 or more cups per day).

62. Kono S, Shinchi K, Ikeda N, Yanai F, Imanishi K. Physical activity, dietary habits and adenomatous polyps of the sigmoid colon: a study of self-defense officials in Japan. *J Clin Epidemiol* 1991;44(11):1255-61.

Physical activity and dietary habits were compared between 80 men with adenomatous polyps of the sigmoid colon and 1148 men with normal colonoscopy among male retiring self-defense officials. Physical activity as expressed in terms of time spent doing strenuous activities during leisure time was inversely related to the risk of adenomatous polyps. Controlling for rank, smoking, alcohol and body mass index (BMI), odds ratios for the categories of 0, 1-59, 60-119 and greater than or equal to 120 minutes per week were 1.0, 0.88, 0.70 and 0.44, respectively (trend $p = 0.015$). Among a limited range of foods and beverages, the consumption of rice, green tea and instant coffee tended to be associated with a decreased risk of adenomatous polyps. Although the associations observed with dietary habits still need to be substantiated, the findings on physical activity lend further evidence to the hypothesis that physical activity may be protective in the development of colon cancer.

63. Kono S. Green tea and gastric cancer in Japan. *N Engl J Med* 2001;344:1867-8.

Consumption of 10 cups or more green tea per day is necessary to reduce the incidence of stomach cancer. A comment on an article by Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Green tea and the risk of gastric cancer in Japan. *N Engl J Med* 2001;344(9):632-6.

64. Koo LC. Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. *Nutr Cancer*. 1988;11(3):155-72.

Department of Community Medicine, University of Hong Kong.

This describes a retrospective study in which 88 lung cancer patients and 137 district-matched controls were interviewed concerning the effects of diet on lung cancer risk among Hong Kong Chinese women who never smoked tobacco. Those in the lowest tertile of consuming fresh fruit or fresh fish had statistically significant adjusted relative risks (RRs) of 2.4 and 2.8, respectively. The protective effects of diet, i.e., higher consumption of leafy green vegetables, carrots, tofu, fresh fruit, and fresh fish, were confined mostly to those with adenocarcinoma or large cell tumors. Only fresh fruit was found to positively, and smoked meats to negatively, affect the risk of squamous or small cell tumors. Foods high in vitamin C, retinol, and calcium seemed to exert larger effects. Subjects from larger households were shown to be more frequent consumers of fresh vegetables, fruit, and fish. Because the lifetime weighted household size could be used as a

surrogate index of past dietary quality, when it was combined with current dietary intakes of fresh fruit, the RR increased as either factor decreased in a dose-response manner. The adjusted RR was 5.8 at the lowest level. Further testing of the validity of the lifetime weighted household size as an index of past dietary quality is needed.

65. Kunze E, Chang-Claude J, Frentzel-Beyme R. Life style and occupational risk factors for bladder cancer in Germany. A case-control study. *Cancer*. 1992 Apr 1;69(7):1776-90.

A hospital-based, case-control study of 531 male and 144 female matched pairs was conducted in Germany to analyze the role of nonoccupational and occupational risk factors in the etiology of tumors of the lower urinary tract (bladder cancer). Smoking of cigarettes was associated with an odds ratio (OR) of 3.6 for men and 3.2 for women, compared with not smoking and showed a significant dose- and time-response relationship for both sexes. Heavy pipe smoking significantly increased the risk (OR = 1.9 in men), and smoking of cigars did not alter the risk of bladder cancer. Controlling for smoking, a significantly twofold or more increase in risk was found for heavy consumption of coffee in both sexes and for heavy intake of beer in males. Increasing levels of total fluid intake were associated with increasing, smoking-adjusted risks in men. Significant associations were found for chronic infection of the lower urinary tract (OR = 1.8), familial history of bladder cancer (OR = 2.5), and frequent consumption of high fat meals (OR = 1.4) among men and for frequent consumption of canned food in both sexes (OR = 1.7 for males, 2.4 for females). With regard to occupational history, significantly elevated odds ratios were found for ever-employment in the printing (5.0), plastics and synthetics (2.6), rubber (2.5), mining (2.0), and dyestuffs (1.9) industries, for exposure to spray paints (2.9), zinc (2.3), chromium/chromate (2.2), oils (1.5), petroleum (1.4), stone dust (1.4) and metal dust/fumes (1.3), and for occupation as mining worker (2.0) and truck driver (1.8) among men. Multivariate logistic regression analysis showed significant contribution of coffee and beer drinking, ingestion of canned food, and familial occurrence of urothelial tumors to the risk of bladder cancer in men after accounting for the effects of tobacco smoking, occupational exposures, and a history of bladder infection. These other variables did not influence the risk attributable to occupational exposures.

66. La Vecchia C, Negri E, Decarli A, D'Avanzo B, Liberati C, Franceschi S. Dietary factors in the risk of bladder cancer. *Nutr Cancer*. 1989;12(1):93-101.

The relationship between selected dietary factors and the risk of bladder cancer was investigated in a case-control study conducted in northern Italy. The study included 163 cases and 181 controls who were hospitalized for acute, nonneoplastic or urinary tract diseases. The frequency of consumption of green vegetables and carrots was lower in the cases; thus, the estimated relative risks for the upper vs. the lower tertiles were 0.6 for green vegetables and 0.5 for carrots. Significant inverse trends in risk emerged with estimated carotenoid (as well as retinoid) intake. The apparent protection conveyed by vitamin A was stronger in current smokers. The risk of bladder cancer was not related to scores of fat and measures of alcohol consumption; the risk was elevated in coffee drinkers (although there was no tendency to rise with higher consumption), but it was reduced in tea drinkers. These findings were not explainable in terms of selection, information, or confounding bias. Thus, although available information is too uncertain for any

precise definition of specific (micro)nutrients related to bladder cancer risk, the confirmation that several aspects of a less-affluent diet adversely affect the risk is still of interest in terms of a better understanding of bladder carcinogenesis.

67. La Vecchia C, Negri E, Franceschi S, D'Avanzo B, Boyle P. Tea consumption and cancer risk. *Nutr Cancer*. 1992;17(1):27-31.

The relationship between tea consumption and cancer risk has been analyzed using data from an integrated series of case-control studies conducted in northern Italy between 1983 and 1990. The dataset included 119 histologically confirmed cancers of the oral cavity and pharynx, 294 of the esophagus, 564 of the stomach, 673 of the colon, 406 of the rectum, 258 of the liver, 41 of the gallbladder, 303 of the pancreas, 149 of the larynx, 2,860 of the breast, 567 of the endometrium, 742 of the ovary, 107 of the prostate, 365 of the bladder, 147 of the kidney, 120 of the thyroid, and a total of 6,147 controls admitted to hospital for acute nonneoplastic conditions unrelated to long-term dietary modifications. Multivariate relative risks (RR) for tea consumption were derived after allowance for age, sex, area of residence, education, smoking, and coffee consumption. All the estimates for tea consumption were close to unity, the highest values being 1.4 for rectum, gallbladder, and endometrium. There was no association with cancers of the oral cavity (RR = 0.6), esophagus (RR = 1.0), stomach (RR = 1.0), bladder (RR = 0.8), kidney (RR = 1.1), prostate (RR = 0.9), or any other site considered. Although in northern Italy tea was consumed daily by only a limited proportion of the population, this integrated series of studies offers further reassuring evidence on the relationship between tea and cancer risk.

68. La Vecchia C, Talamini R, Decarli A, Franceschi S, Parazzini F, Tognoni G. Coffee consumption and the risk of breast cancer. *Surgery*. 1986 Sep;100(3):477-81.

The relationship of breast cancer to coffee drinking habits was evaluated in a case-control study of 616 women with breast cancer and 616 control subjects with nonmalignant disorders, apparently unrelated to coffee consumption. Compared with women who had never drunk coffee, the relative risk estimates for those women who drank less than two, two or three, and four or more cups each day were 1.5, 1.3, and 1.0, respectively. There was no apparent association with duration of consumption or use of other methylxanthine-containing beverages. The results were not modified by several potential confounding factors, including the major risk factors for breast cancer. The findings suggest that coffee consumption does not increase the risk of malignant neoplasms of the breast.

69. Le Marchand L, Murphy SP, Hankin JH, Wilkens LR, Kolonel LN. Intake of flavonoids and lung cancer. *J Natl Cancer Inst*. 2000 Jan 19;92(2):154-60.
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BACKGROUND: To investigate the possible relationship between intake of flavonoids-powerful dietary antioxidants that may also inhibit P450 enzymes-and lung cancer risk, we

conducted a population-based, case-control study in Hawaii. **METHODS:** An in-person interview assessed smoking history and usual intake of 242 food items for 582 patients with incident lung cancer and 582 age-, sex-, and ethnicity-matched control subjects. Subjects who donated a blood sample were genotyped for the P450 enzyme variant allele CYP1A1*2 by use of a polymerase chain reaction-based method. Logistic regression analysis was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). All P values are two-sided. **RESULTS:** After adjusting for smoking and intakes of saturated fat and beta-carotene, we found statistically significant inverse associations between lung cancer risk and the main food sources of the flavonoids quercetin (onions and apples) and naringin (white grapefruit). The lung cancer OR for the highest compared with the lowest quartile of intake was 0.5 (95% CI = 0.3-0.9) for onions (P for trend = .001) and 0.6 (95% CI = 0.4-1.0) for apples (P for trend = .03). The OR for the highest compared with the lowest tertile of intake for white grapefruit was 0.5 (95% CI = 0.2-0.9) (P for trend = .02). No association was found for important food sources of other flavonoids. Using published food-composition data for flavonoids, we found an inverse association between intake of quercetin and risk of lung cancer (P for trend = .07) that appears consistent with associations for its food sources. The effect of onions was particularly strong against squamous cell carcinoma (a cell type specifically associated with CYP1A1*2 in our study) and was modified by the CYP1A1 genotype, suggesting that CYP1A1 may play a role in this association. **CONCLUSION:** If replicated, particularly in prospective studies, these findings would suggest that foods rich in certain flavonoids may protect against certain forms of lung cancer and that decreased bioactivation of carcinogens by inhibition of CYP1A1 should be explored as underlying mechanisms.

70. Lee HH, Wu HY, Chuang YC, Chang AS, Chao HH, Chen KY, Chen HK, Lai GM, Huang HH, Chen CJ. Epidemiologic characteristics and multiple risk factors of stomach cancer in Taiwan. *Anticancer Res* 1990 Jul-Aug;10(4):875-81.

This is a hospital-based matched case-control study carried out in Taipei metropolitan areas showing a positive association of stomach cancer with blood type A, chronic gastric diseases, cigarette smoking, alcohol drinking, green tea drinking (only 10 patients with a questionable significant *p* value between 0.05 and 0.10), as well as consumption of salted meat, cured meat, smoked food, fried food and fermented beans. It included 210 stomach cancer patients in the study, in which green tea was used in less than 2% of hospital controls. Because Chinese patients with various illnesses often avoid tea drinking when certain medications are taken, particularly herbal medicines, and may be encouraged to consume more nutritious drinks (e.g., chicken soup and milk), the findings from this study are difficult to interpret (see comments in Author Reply of Ref. # 23 by Bu-Tian Ji et al.). Furthermore, in Taiwan and southern China oolong teas are customarily referred to as green tea by the general public and tea merchants. Traditionally, southern Chinese and Taiwanese tend to avoid drinking green tea because of its notorious "harmful" physiological effects in depleting body fat during famine years, a remarkably accurate observation made by the Chinese peasants over the past three centuries. This fact is reflected in Table VI of this article that the ratios of half-processed tea drinkers: green tea drinkers were 70:10 in the Case Number group and 285:14 in the Control Number group, respectively. In view of these confounding factors, this report is not classified as an epidemiological study primarily based on green tea.

71. Lu CM, Lan SJ, Lee YH, Huang JK, Huang CH, Hsieh CC. Tea consumption: fluid intake and bladder cancer risk in Southern Taiwan. *Urology*. 1999 Nov;54(5):823-8.
Department of Urology, Tian-Sheng Memorial Hospital, Pingtung, Taiwan.

OBJECTIVES: To determine whether tea consumption and intake of other beverages increases bladder cancer risk. **METHODS:** A case-control study was conducted in Kaohsiung, Taiwan between August 1996 and June 1997. Index patients studied were consecutive patients with histologically confirmed, newly diagnosed bladder cancer in two major hospitals. For each patient, 4 controls were selected from patients with non-neoplastic and nonurologic diseases undergoing surgical operations in the same hospital and individually matched by sex, age, and date of admission. Using a structured questionnaire, a trained interviewer interviewed 40 patients and 160 controls. Conditional logistic regression analysis adjusting for ethnicity, family history, and smoking status and matching variables were used to estimate the odds ratio (OR) and 95% confidence interval (CI). **RESULTS:** Tea consumption overall was associated with increased bladder cancer risk (OR 3.29, 95% CI 1.34 to 8.05). Compared with non-tea drinkers, the odds ratios of bladder cancer for oolong tea drinkers was 3.00 (95% CI 1.20 to 7.47); for non-oolong tea drinkers (black and/or other green tea), it was 14.86 (95% CI 2.13 to 103.83). The risk was greater among those who began to drink tea before age 40 (OR 9.50, 95% CI 2.39 to 37.75) and those who had been drinking tea for more than 30 years (OR 17.75, 95% CI 3.00 to 105.17). Coffee, tap water, and alcohol consumption were associated with a slightly increased risk, and both soy juice and rice juice consumption were associated with reduced risk; none of these odds ratio estimates were statistically significant, however. **CONCLUSIONS:** Our results suggest that tea consumption is associated with an increased risk of bladder cancer.

72. Lubin F, Ron E, Wax Y, Modan B. Coffee and methylxanthines and breast cancer: a case-control study. *J Natl Cancer Inst*. 1985 Mar;74(3):569-73.

A dietary case-control study based on 818 newly diagnosed breast cancer (BC) patients was conducted in Israel between 1975 and 1978. The role of coffee and total methylxanthine intake from coffee, tea, cola, chocolate, and cocoa drinks was evaluated in the BC patients as compared to that in two matched control populations [surgical controls (SC) and neighborhood controls (NC)]. Because it has been suggested that caffeine enhances mammary carcinogenesis in rats fed high polyunsaturated fat diets, analysis was done also in relation to fat consumption. When comparison was done to both matched control groups, a nonsignificant negative association was found between consumption of cups of coffee and BC (odds ratios of greater than or equal to 4 cups of coffee/day vs. less than or equal to 1 per week = 0.6 for BC/NC and 0.7 for BC/SC). This association was observed in all 3 ethnic subgroups studied. The pattern was stronger among the high-fat consumers after controlling for several hormonal confounding factors (two-tailed P-value for linear trend = 0.06 for SC and P = 0.05 for NC). In addition, when the consumption of methylxanthine of BC patients was compared to that of benign breast patients, adjusted by age and ethnic group, a diminished risk was found (odds ratio for BC of the highest level of methylxanthine vs. lowest level = 0.59).

73. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas cancer and smoking, beverage consumption, and past medical history. *J Natl Cancer Inst.* 1986 Jan;76(1):49-60.

Four hundred and ninety pancreas cancer patients representative of confirmed cases in Los Angeles County residents of working age were compared to healthy controls individually matched by age, sex, race, and neighborhood. Home interviews were conducted on occupation, smoking, food and beverage consumption, and medical history. Cigarette smoking was a strong and consistent predictor of pancreas cancer occurrence; the effect disappeared after a decade of nonsmoking, and there was no increase in risk among current smokers as daily dose increased. There was no link between pancreas cancer and past consumption of tea, carbonated beverages, beer, or spirits; and an association with coffee consumption was inconsistent. A strong association between pancreas cancer and history of subtotal gastrectomy at any past time could not be explained by chance or any other factor. Pancreas cancer patients had experienced fewer allergies of any kind.

74. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and cancer of the pancreas. *N Engl J Med.* 1981 Mar 12;304(11):630-3.

We questioned 369 patients with histologically proved cancer of the pancreas and 644 control patients about their use of tobacco, alcohol, tea, and coffee. There was a weak positive association between pancreatic cancer and cigarette smoking, but we found no association with use of cigars, pipe tobacco, alcoholic beverages, or tea. A strong association between coffee consumption and pancreatic cancer was evident in both sexes. The association was not affected by controlling for cigarette use. For the sexes combined, there was a significant dose-response relation (P approximately 0.001); after adjustment for cigarette smoking, the relative risk associated with drinking up to two cups of coffee per day was 1.8 (95% confidence limits, 1.0 to 3.0), and that with three or more cups per day was 2.7 (1.6 to 4.7). This association should be evaluated with other data; if it reflects a causal relation between coffee drinking and pancreatic cancer, coffee use might account for a substantial proportion of the cases of this disease in the United States.

75. McCredie M, Ford JM, Stewart JH. Risk factors for cancer of the renal parenchyma. *Int J Cancer.* 1988 Jul 15;42(1):13-6.

A case-control study of cancer of the renal parenchyma (360 cases and 985 controls) investigated lifestyle and dietary risk factors by means of a questionnaire survey. A lifetime history concerning urological disease and consumption of analgesics, tobacco, and prescribed medicines, was obtained together with current dietary and demographic information. Estimates of relative risk were calculated using logistic regression. Statistically significant associations were found with phenacetin-containing analgesics, urological disease and increasing consumption of milk. No association was found with consumption of aspirin, paracetamol, prescribed medicines, tea, coffee or animal proteins other than milk, or with the type of fat or oil used for cooking or spreading. The association with tobacco just failed to reach significance.

76. McLaughlin JK, Mandel JS, Blot WJ, Schuman LM, Mehl ES, Fraumeni JF Jr. A population-based case-control study of renal cell carcinoma. *J Natl Cancer Inst.* 1984 Feb;72(2):275-84.

A population-based case-control study of renal cell carcinoma (495 cases and 697 controls) in the Minneapolis-St. Paul seven-county metropolitan area implicated cigarette smoking as a risk factor with an odds ratio (OR) among men of 1.6 (95% confidence intervals: 1.1-2.4) and among women of 1.9 (1.3-3.0). A statistically significant dose response was observed in both sexes for pack-years of cigarette use. On the basis of calculations of attributable risk, it was estimated that 30% of renal cell cancers among men and 24% among women were due to smoking. High relative adult weight as measured by the body mass index (BMI) was found to be a major risk factor among women but not among men, with those in the highest 5% of the BMI having an OR of 5.9 (1.8-20.4) in comparison to the lowest quartile. This association with excess weight was not seen at age 20, but it became more pronounced with increasing age, suggesting that the primary influence of weight gain is during the late stages of renal carcinogenesis. Excess risks were also related to ethnic background (particularly, German), which may account in part for the elevated incidence of renal cancer in the North Central area of the United States. In addition, positive associations were observed for long-term use of phenacetin-containing analgesics, heavy meat consumption, and heavy tea drinking (females only). An occupational clue was provided by an increased risk for exposure to petroleum, tar, and pitch products. Excesses of certain urologic and cardiovascular diseases were also observed among the cases compared to controls.

77. Memik F, Nak SG, Gulten M, Ozturk M. Gastric carcinoma in northwestern Turkey: epidemiologic characteristics. *J Environ Pathol Toxicol Oncol.* 1992 Sep-Oct;11(5-6):335-8.

We studied 252 newly diagnosed gastric cancer patients seen at our institution between 1977 and 1991 and compared the findings with 609 age- and gender-matched controls. There was no difference in the mean age and the M:F ratio. Most of our patients were rural dwellers from a low socio-economic group. The proximal portion of the stomach was most often involved. No statistically significant differences were found with regard to the use of coffee, alcohol, starchy food, and fresh fruits. The relative risk for gastric cancer was significantly higher statistically in individuals who consumed only small amounts of vegetables and bread. Although an increased relative risk was noted between gastric cancer and the amount of milk and meat consumed, this appears to have been fortuitous: an increased consumption of milk may have been due to patients' attempts to alleviate symptoms, and a low meat intake most likely was due to the low income level of the majority of our patients.

78. Mendilaharsu M, De Stefani E, Deneo-Pellegrini H, Carzoglio JC, Ronco A. Consumption of tea and coffee and the risk of lung cancer in cigarette-smoking men: a case-control study in Uruguay. *Lung Cancer.* 1998 Feb;19(2):101-7.

Registro Nacional de Cancer, Instituto Nacional de Oncologia, Montevideo, Uruguay.

This study investigated the effect of drinking tea or coffee on the lung cancer risk of male cigarette smokers in a case-control in Uruguay. Four hundred and twenty-seven lung cancer cases were frequency matched on age and residence with 428 hospitalized controls suffering from conditions unrelated to tobacco smoking and diet. Whereas coffee drinking had no effect on the lung cancer risk of the cigarette-smoking men in this study, black tea consumption decreased this risk. Heavy drinkers of tea (two or more cups of tea per day) were associated with a reduced risk of 0.34 (95% CI 0.14-0.84). This protective effect was more evident among Kreyberg I tumors (squamous cell and small cell) and among light smokers. Possible sources of bias and mechanisms of action are discussed.

79. Mettlin C. Milk drinking, other beverage habits, and lung cancer risk. *Int J Cancer*. 1989 Apr 15;43(4):608-12.

Dept. of Cancer Control and Epidemiology, Roswell Park Memorial Institute, Buffalo, NY 14263.

The reported beverage habits of 569 lung cancer patients and 569 control patients admitted to Roswell Park Memorial Institute (RPMI) were studied, 355 male cases and 214 female cases being matched to controls within strata of age and residence. Smoking history and an index of vitamin A from vegetables had significant, dose-response associations with risk. Animal fat intake as measured by an index of animal fats from meats showed elevated risks which were not significant. Three vegetables rich in vitamin A and 3 meats contributing to the animal fat index were, individually, associated with lung cancer risk. Frequency of consumption of milk, coffee, tea, soft drinks and alcoholic beverages was studied in multiple logistic regression analyses which controlled for smoking history, intake of vitamin A from vegetables and education level. Subjects reporting consumption of whole milk 3 or more times daily had a 2-fold increase in lung cancer risk compared to those who reported never drinking whole milk (RR = 2.14). The same frequency of intake of reduced-fat milk was associated with a significant protective effect (RR = .54). Significant risk variations were observed for other beverages but, with the exception of frequencies of reported diet cola and decaffeinated coffee intake, dose-response patterns were not evident.

80. Michaud DS, Spiegelman D, Clinton SK, Rimm EB, Curhan GC, Willett WC, Giovannucci EL. Fluid intake and the risk of bladder cancer in men. *N Engl J Med*. 1999 May 6;340(18):1390-7.

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BACKGROUND: Studies in animals have shown that the frequency of urination is inversely associated with the level of potential carcinogens in the urothelium. In humans, an increase in total fluid intake may reduce contact time between carcinogens and urothelium by diluting urinary metabolites and increasing the frequency of voiding. The data on fluid intake in relation to the risk of bladder cancer are inconclusive. **METHODS:** We examined the relation between total fluid intake and the risk of bladder cancer over a period of 10 years among 47,909 participants in the prospective Health Professionals Follow-up Study. There were 252 newly

diagnosed cases of bladder cancer during the follow-up period. Information on total fluid intake was derived from the reported frequency of consumption of the 22 types of beverages on the food-frequency questionnaire, which was completed by each of the 47,909 participants who were free of cancer in 1986. Logistic-regression analyses were performed to adjust for known and suspected risk factors for bladder cancer. RESULTS: Total daily fluid intake was inversely associated with the risk of bladder cancer; the multivariate relative risk was 0.51 (95 percent confidence interval, 0.32 to 0.80) for the highest quintile of total daily fluid intake (>2531 ml per day) as compared with the lowest quintile (<1290 ml per day). The consumption of water contributed to a lower risk (relative risk, 0.49 [95 percent confidence interval, 0.28 to 0.86] for > or =1440 ml [6 cups] per day vs. <240 ml [1 cup] per day), as did the consumption of other fluids (relative risk, 0.63 [95 percent confidence interval, 0.39 to 0.99] for >1831 ml per day vs. <735 ml per day). CONCLUSIONS: A high fluid intake is associated with a decreased risk of bladder cancer in men.

81. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS.
Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev.* 2001 May;10(5):429-37.

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Although most prospective cohort studies do not support an association between coffee consumption and pancreatic cancer, the findings for alcohol are inconsistent. Recently, a large prospective cohort study of women reported statistically significant elevations in risk of pancreatic cancer for both coffee and alcoholic beverage consumption. We obtained data on coffee, alcohol, and other dietary factors using semiquantitative food frequency questionnaires administered at baseline (1986 in the Health Professionals Follow-Up Study and 1980 in the Nurses' Health Study) and in subsequent follow-up questionnaires. Data on other risk factors for pancreatic cancer, including cigarette smoking, were also available. Individuals with a history of cancer at study initiation were excluded from all of the analyses. During the 1,907,222 person-years of follow-up, 288 incident cases of pancreatic cancer were diagnosed. The data were analyzed separately for each cohort, and results were pooled to compute overall relative risks (RR). Neither coffee nor alcohol intakes were associated with an increased risk of pancreatic cancer in either cohort or after pooling the results (pooled RR, 0.62; 95% confidence interval, 0.27-1.43, for >3 cups of coffee/day versus none; and pooled RR, 1.00; 95% confidence interval, 0.57-1.76, for > or = 30 grams of alcohol/day versus none). The associations did not change with analyses examining different latency periods for coffee and alcohol. Similarly, no statistically significant associations were observed for intakes of tea, decaffeinated coffee, total caffeine, or alcoholic beverages. Data from these two large cohorts do not support any overall association between coffee intake or alcohol intake and risk of pancreatic cancer.

82. Miller AB, Howe GR, Jain M, Craib KJ, Harrison L. Food items and food groups as risk factors in a case-control study of diet and colo-rectal cancer. *Int J Cancer.* 1983 Aug 15;32(2):155-61.

The contributions of food items and food groups as risk factors in a previously reported case-control study of diet and colo-rectal cancer have been analyzed. The study included 348 patients with colon cancer, 194 with rectal cancer, 542 neighbourhood controls individually matched to the cases on the basis of age and sex and a second control series of 535 surgical hospital controls frequency matched to the cases. For colon cancer, as in the previous analysis, the major risk factor was saturated fat, individual food items or groups failing to make a significant contribution to the risk. In particular there was no protective effect of dietary fibre and, for cruciferous vegetables, only a minor protective effect in females. No individual cruciferous vegetable made an important contribution to this effect. For rectal cancer, on the other hand, a significant effect of saturated fat, independent of other food items or groups, was only found for females in the highest consumption category. For males, consumption of eggs, beef and veal significantly increased risk but not consumption of pork, while for females, there was a non-significant increase in risk with consumption of eggs, no increased risk with consumption of beef or veal and a significantly increased risk with consumption of pork. There was no protective effect of dietary fibre or of cruciferous vegetables for rectal cancer, but in females, there was a significantly increased risk for consumption of beer, though this was somewhat reduced when controlled for consumption of saturated fat. There was no indication of an effect of alcohol in either sex or of beer in males. Thus, these results confirm the previous report in showing a significant effect of saturated fat in increasing risk of colon cancer but suggest a contribution of meats to risk of rectal cancer.

83. Miller CT, Neutel CI, Nair RC, Marrett LD, Last JM, Collins WE. Relative importance of risk factors in bladder carcinogenesis. *J Chronic Dis.* 1978 Jan;31(1):51-6.

Tea consumption was not found to be related to bladder cancer risk.

84. Mizuno S, Watanabe S, Nakamura K, Omata M, Oguchi H, Ohashi K, Ohyanagi H, Fujiki T, Motojima K. A multi-institute case-control study on the risk factors of developing pancreatic cancer. *Jpn J Clin Oncol.* 1992 Aug;22(4):286-91.

A multi-institute, hospital-based, case-control study on pancreatic cancer was carried out to examine its association with preceding diseases, cigarette smoking, alcohol drinking and dietary factors. Analyses were based on 124 newly diagnosed exocrine pancreatic cancer cases and sex-, age- and institute-matched hospital controls in seven hospitals in Japan. Cigarette smoking showed a positive association with the risk of developing pancreatic cancer. Especially among smokers, a risk enhancing effect of involuntary/passive smoking prior to twenty years of age was observed ($P < 0.05$). No consistent associations were found with coffee, black tea or alcohol consumption. Among dietary factors, favoring food of a salty taste and drinking green tea five cups per day or more were positively associated with the risk. Drinking milk and eating fish everyday were inversely associated with the risk.

85. Morgan RW, Jain MG. Bladder cancer: smoking, beverages and artificial sweeteners. *Can Med Assoc J.* 1974 Nov 16;111(10):1067-70.

Tea and coffee intake did not increase the relative risk of bladder cancer.

86. Mori M, Hariharan M, Anandakumar M, Tsutsumi M, Ishikawa O, Konishi Y, Chellam VG, John M, Praseeda I, Priya R, Narendranathan M. A case-control study on risk factors for pancreatic diseases in Kerala, India. *Hepatogastroenterology.* 1999 Jan-Feb;46(25):25-30.

Department of Community Health Science, Saga Medical School, Japan.

BACKGROUND/AIMS: We simultaneously conducted case-control studies, in Kerala of South India, on chronic calcific pancreatitis of the tropics (CCPT), pancreatic ductal adenocarcinoma (PDA) with CCPT, and PDA alone to assess similarity of and difference between their risk factors. **METHODOLOGY:** Cases with one of these diseases were identified at the Trivandrum Medical College (TMC) Hospital, in Kerala, from 1994 to 1996. Controls were selected from healthy hospital visitors of the TMC Hospital by individual age (within +/- 3 years) and sex-matched with the index case. Odds ratios and their 95% confidence intervals for potential risk factors were calculated. **RESULTS:** Frequent consumption of cassava was positively associated with the risk of PDA with CCPT. Heavy cigarette smoking and drinking large amounts of coffee and/or tea everyday were positively related to the risk of PDA alone. Frequent consumption of vegetables and/or fruits was correlated to the decreased risk of PDA alone. **CONCLUSIONS:** Risk factors as well as preventive factors seem to be different between PDA with CCPT and PDA alone. Further study is necessary, especially to clarify the prognostic factors which would induce pancreatic malignancy in patients with CCPT.

87. Mu LN, Zhou XF, Ding BG, Wang RH, Zhang ZF, Chen CW, Wei GR, Zhou XM, Jiang QW, Yu SZ. A case-control study on drinking green tea and decreasing risk of cancers in the alimentary canal among cigarette smokers and alcohol drinkers *Zhonghua Liu Xing Bing Xue Za Zhi.* 2003 Mar;24(3):192-5.

OBJECTIVE: To explore the role of green tea in decreasing the risks of gastric cancer, liver cancer, esophageal cancer among alcohol drinkers or cigarette smokers. **METHODS:** A population based case-control study was conducted in Taixing, Jiangsu province. **RESULTS:** In Taixing city, identified cases of stomach, liver and esophageal cancers were chosen with informed consent. The numbers were 206, 204, 218 respectively. Controls were chosen from normal population having lived in the area for longer than 10 years, also with informed consent. Green tea drinking seemed to have decreased 81%, 78%, 39% risk for the development of gastric cancer, liver cancer and esophageal cancer among alcohol drinkers. It might also have decreased 16%, 43%, 31% on the risks of developing the three kinds of cancers among cigarette smokers. Interaction assessment showed that drinking green tea could significantly decrease the risk of gastric cancer and liver cancer among alcohol drinkers, with ORs of interaction item 0.23 (95% CI: 0.10 - 0.55) and 0.25 (95% CI: 0.11 - 0.57) respectively. **CONCLUSION:** Habit of drinking green tea seemed to have significant protective effects on the development of both gastric and

liver cancer among alcohol drinkers while, green tea also having some protective effect on esophageal cancer among alcohol drinkers and on three kinds of cancers among cigarette smokers.

88. Munoz SE, Navarro A, Lantieri MJ, Fabro ME, Peyrano MG, Ferraroni M, Decarli A, La Vecchia C, Eynard AR. Alcohol, methylxanthine-containing beverages, and colorectal cancer in Cordoba, Argentina. *Eur J Cancer Prev.* 1998 Jun;7(3):207-13.

Instituto de Biologia Celular, Facultad de Ciencias Medicas, Universidad Nacional de Cordoba, Argentina.

The relationship between social class indicators, body mass index (BMI), selected life-style habits (alcohol, coffee, mate and tea drinking) and colorectal cancer was investigated in a case-control study conducted between 1993 and 1997 in Cordoba, Argentina, a relatively high mortality area of colorectal cancer. Cases were 190 patients below age 80 years with incident, histologically confirmed colorectal adenocarcinomas, and controls were 393 patients admitted to hospital for a wide spectrum of acute, non-neoplastic disorders. Higher social class, based on occupation of the head of the household, was significantly associated with colorectal cancer risk: the odds ratios (OR) and 95% confidence intervals (95% CI) were 1.9 (1.2-2.9) for intermediate and 2.0 (1.2-3.4) for the highest as compared to the lowest social class individuals. When compared with subjects whose BMI was < 25 kg/m², the OR was 1.1 (0.7-1.6) for those with BMI 25 to 29 kg/m², and 1.3 (0.7-2.3) for those ≥ 30. In comparison with alcohol abstainers, the OR was 2.8 (1.6-5.1) for drinkers, and there was a significant trend in risk with dose. The association was observed with wine (the most common alcoholic beverage in Argentina), as well as for beer and spirits. The consumption of coffee, mate and tea was not significantly related to colorectal cancer, but the ORs were below unity (0.9 (0.7-1.3) for coffee, 0.9 (0.6-1.2) for mate and 0.8 (0.6-1.2) for tea drinkers). The relationship between social class, alcohol drinking and colorectal cancer were consistent across strata of sex and age. This study confirms that colorectal cancer has positive social class correlates. The association with alcohol drinking is apparently stronger than previously reported, and may be due to the role of chance and/or peculiar correlates of alcohol drinking in this Argentinean population.

89. Nagano J, Kono S, Preston DL, Mabuchi K. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). *Cancer Causes Control* 2001;12:501-8. Department of Epidemiology, Radiation Effects Research Foundation, Hiroshima, Japan.

OBJECTIVES: Laboratory and animal studies have shown a protective effect of green tea on cancer of different sites, but epidemiological evidence is limited and inconclusive. This prospective study in Japan examined the association between green tea consumption and cancer incidence. **METHODS:** Subjects were 38,540 people (14,873 men, mean age 52.8 years; 23,667 women, mean age 56.8 years) who responded to a mail survey carried out between 1979 and 1981. A self-administered questionnaire ascertained consumption frequency of green tea using precoded answers (never, once per day, twice to four times per day, and five or more times per day). Follow-up continued until 31 December 1994. The study analyzed solid cancers (n =

3881); hematopoietic cancers (188); cancers of all sites combined (4069); and cancer of specific sites with more than 100 cases, i.e. stomach (901), colon (432), rectum (193), liver (418), gallbladder (122), pancreas (122), lung (436), breast (281), and bladder (122). Poisson regression was used to allow for city, gender, age, radiation exposure, smoking status, alcohol drinking, body-mass index, education level, and calendar time. RESULTS: Green tea consumption was virtually unrelated to incidence of cancers under study. The relative risks of all cancers for those consuming green tea twice to four times per day and five or more times per day were 1.0 (95% confidence interval 0.91-1.1) and 0.98 (0.88-1.1), respectively, as compared with those consuming green tea once per day or less. CONCLUSION: Our findings do not provide evidence that regular green tea consumption is related to reduced cancer risks. This failure may be due to some crudeness in the assessment of green tea intake; green tea consumption was determined only in terms of self-reported daily frequency of drinking, and the highest category was five or more cups per day. Bioactivity of a cup of green tea obviously differs by the amount of green tea leaves used to brew it and the frequency of renewing a tea batch in the pot. In Shizuoka prefecture, which has the highest production of green tea leaves in Japan, residents of towns with low mortality from stomach cancer were found not only to drink green tea more frequently, but also to renew tea leaves more frequently than those of a town with high mortality from stomach cancer.

90. Nakachi K, Eguchi H, Imai K. Can teatime increase one's lifetime? *Ageing Res Rev* 2003;2:1-10.

Department of Epidemiology, Radiation Effects Research Foundation, Hijiya, Minami-ku, 732-0815, Hiroshima, Japan.

Lifestyle-related diseases, including cancer and cardiovascular disease, are also characterized as aging-related diseases, where aging may be the most potent causal factor. In light of this, prevention of lifestyle-related diseases will depend on slowing the aging process and avoiding the clinical appearance of the diseases. Green tea is now accepted as a cancer preventive on the basis of numerous in vitro, in vivo and epidemiological studies. In addition, green tea has also been reported to reduce the risk of cardiovascular disease. The authors found an apparent delay of cancer onset/death and all cause deaths associated with increased consumption of green tea, specifically in ages before 79 in a prospective cohort study of a Japanese population with 13-year follow-up data. This is consistent with analyses of age-specific cancer death rate and cumulative survival, indicating a significant slowing of the increase in cancer death and all cause death with aging. These results indicate that daily consumption of green tea in sufficient amounts will help to prolong life by avoiding pre-mature death, particularly death caused by cancer.

91. Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. *BioFactors* 2000;13(1-4):49-54.

Saitama Cancer Center Research Institute, Ina, Japan. The significance of drinking green tea in prevention of two of the main lifestyle-related diseases, cancer and cardiovascular disease, was demonstrated in terms of a prospective cohort study on a total of 8,552 general residents in

Saitama Prefecture, Japan. On the basis of the follow-up study, we revealed decreased relative risk of cancer incidence for those consuming over 10 cups a day, compared with those consuming below 3 cups: 0.54 (95% confidence interval, 0.22-1.34) for men, 0.57 (0.34-0.98) for women, and 0.59 (0.35-0.98) for both sexes. Furthermore, a significant delay in cancer onset was associated with increased consumption of green tea. Next, decreased relative risk of death from cardiovascular disease was 0.58 (0.34-0.99) for men, 0.82 (0.49-1.38) for women, and 0.72 (0.60-1.04) for members of both sexes consuming over 10 cups a day. Finally, we evaluated the life-prolonging effects of drinking green tea on cumulative survival, using the life table. The relative risk for cancers of the colorectum, liver and stomach was most notably reduced.

92. Nakachi K, Suemasu K, Suga K, Takeo T, Imai K, Higashi Y. Influence of drinking green tea on breast cancer malignancy among Japanese patients. *Jpn J Cancer Res.* 1998 Mar;89(3):254-61.

Inhibitory effects of green tea on carcinogenesis have been investigated in numerous laboratory studies using (-)-epigallocatechin gallate (EGCG) or crude green tea extract, and there is also some epidemiologic evidence. Further, EGCG has been reported to inhibit the growth of cancer cells, lung metastasis in an animal model, and urokinase activity. In this study, we first examined the association between consumption of green tea prior to clinical cancer onset and various clinical parameters assessed at surgery among 472 patients with stage I, II, and III breast cancer. We found that increased consumption of green tea was closely associated with decreased numbers of axillary lymph node metastases among premenopausal patients with stage I and II breast cancer and with increased expression of progesterone receptor (PgR) and estrogen receptor (ER) among postmenopausal ones. Since these are potential prognostic factors, we then investigated the prognosis of breast cancer with special reference to consumption of green tea, in a follow-up study of these patients. We found that increased consumption of green tea was correlated with decreased recurrence of stage I and II breast cancer ($P < 0.05$ for crude disease-free survival); the recurrence rate was 16.7 or 24.3% among those consuming ≥ 5 cups or ≤ 4 cups per day, respectively, in a seven-year follow-up of stage I and II breast cancer, and the relative risk of recurrence was 0.564 (95% confidence interval, 0.350-0.911) after adjustment for other lifestyle factors. However, no improvement in prognosis was observed in stage III breast cancer. Our results indicate that increased consumption of green tea prior to clinical cancer onset is significantly associated with improved prognosis of stage I and II breast cancer, and this association may be related to a modifying effect of green tea on the clinical characteristics of the cancer.

93. Nomura AM, Kolonel LN, Hankin JH, Yoshizawa CN. Dietary factors in cancer of the lower urinary tract. *Int J Cancer* 1991 May 10;48(2):199-205.

This dietary study was based on 195 male and 66 female cases of lower urinary tract cancer, identified in Hawaii between 1977 and 1986. Each case was matched for sex, age, and ethnic group (Caucasian or Japanese) to 2 population-based controls. There was a decrease in risk with increasing levels of consumption of vitamin C in women ($p = 0.03$) and dark green vegetables in men ($p = 0.02$). When examined by quartile, the odds ratios for the highest quartile of intake

compared to the lowest quartile were 0.4 for women and 0.6 for men, respectively. Although dark green vegetables are a source of carotenoids, the intake of total carotenoids, retinol and total vitamin A was weakly and inconsistently related to risk in both sexes. Among women only, there was also an inverse association with the consumption of regular ground coffee ($p = 0.02$) but not with other types of coffee. Finally, there were no statistically significant or consistent differences between cases and controls in the intake of artificial sweeteners and tea.

94. Notani PN, Jayant K. Role of diet in upper aerodigestive tract cancers. *Nutr Cancer*. 1987;10(1-2):103-13.

A case-control interview study for assessing the role of dietary factors in selected cancers was undertaken in a hospital. Male patients from one community, with cancers of the oral cavity ($n = 278$), pharynx ($n = 225$), esophagus ($n = 236$), and larynx ($n = 80$) formed the case group. Patients diagnosed as not having cancer ($n = 215$) formed one control group, and a comparable sample of individuals from the general population ($n = 177$) formed another control group. All risks were adjusted for subjects' ages and habits of chewing and/or smoking tobacco, which are the two most important risk factors for cancers at these sites. A protective effect was observed with the intake of vegetables (twofold risk in nondaily vs. daily consumers) and fish (two- to threefold risk in those who did not eat at least once a week vs. those who did), and to a certain extent with pulses and buttermilk, in comparison with either one or both control groups. Intake of vegetables and fish were also observed to be risk modifiers for those who chewed and/or smoked tobacco. Lower levels of fat consumption was associated with elevated risk levels. The use of red chili powder emerged as a risk factor for all sites (two- to threefold risk with a dose-response relationship) compared with population controls. Tea drinking was also observed to be a risk factor for esophageal cancers, and to a lesser extent, for pharyngeal cancers.

95. Oguni I, Cheng SJ, Lin PZ, Hara Y. Protection against cancer risk by Japanese green tea (abstract) *Prev Med* 1992; 21: 332.

Statistics on Japanese people indicated that the cancer mortality rate for both males and females in Shizuoka Prefecture, located in central Japan, is much lower than the average for Japanese people. We further investigated this phenomenon epidemiologically and experimentally. The results were as follows. (a) In the midwest areas of Shizuoka Prefecture, where green tea is the staple product, the standardized mortality ratio (SMR) for cancer of all sites and stomach cancer was much lower than the average ratio for Japanese people of both sexes. (b) The survey analysis on green tea intake indicated that the inhabitants of the areas with low SMR due to stomach cancer seemed to have been much more habitual in drinking green tea compared with those of the areas with high SMR. (c) Oral administration of crude extracts of green tea leaves inhibited the growth of mouse sarcoma 180 inoculated into mice. And intraperitoneal administration of (-)-epigallocatechin gallate (the main component of green tea tannin) also suppressed the growths of Ehrlich tumors implanted into mice and the methylcholanthrene-induced tumors implanted into rats. (d) Oral administration of crude green tea extracts inhibited the incidences of the carcinomas in both esophagus and forestomach in mice, induced by in vivo formation of nitrososarcosine from its precursors, sarcosine and sodium nitrite. These results strongly suggested that Japanese green tea plays a role in protecting against cancer risk.

96. Ohno Y, Aoki K, Obata K, Morrison AS. Case-control study of urinary bladder cancer in metropolitan Nagoya. *Natl Cancer Inst Monogr.* 1985 Dec;69:229-34.

We conducted a population-based case-control study of patients with bladder cancer and of controls drawn randomly from the general population of Metropolitan Nagoya and interviewed both groups. The incidence rates of bladder cancer were 2.42 and 7.05/100,000 for females and males, respectively. The analysis, based on 293 patients and 589 controls who were frequency matched for age, sex, and residence, provided the following major findings. Age-adjusted relative risks of 1.89 (1.15-3.10) and 3.53 (1.71-7.27) were found in male and female cigarette smokers, respectively. Significant relative risk was also found in males who drank cocoa. Elevated risk with a dose-response relationship was observed among women who used hair dye and who smoke, but this risk was insignificant, with the disappearance of a dose-response relationship, when it was adjusted for smoking. Age- and smoking-adjusted relative risk of coffee drinking was insignificant with no dose-response relationship. Relative risk of artificial sweetener use was below 1 with adjustment for age and smoking. Intake of alcoholic beverages and cola was insignificantly associated. Reduced risk of significance was suggested for the intake of black tea and matcha (powdered green tea) in females and of fruit juice in males.

97. Ohno Y, Wakai K, Genka K, Ohmine K, Kawamura T, Tamakoshi A, Aoki R, Senda M, Hayashi Y, Nagao K, et al. Tea consumption and lung cancer risk: a case-control study in Okinawa, Japan. *Jpn J Cancer Res.* 1995 Nov;86(11):1027-34.

To disclose the relationship between tea consumption and lung cancer risk, we analyzed the data from a case-control study conducted in Okinawa, Japan from 1988 to 1991. The analysis, based on 333 cases and 666 age-, sex- and residence-matched controls, provided the following major findings. (a) The greater the intake of Okinawa tea (a partially fermented tea), the smaller the risk, particularly in women. For females, the odds ratios (and 95% confidence intervals) for those who consumed 1-4, 5-9, and 10 cups or more of Okinawan tea every day, relative to non-daily tea drinkers, were 0.77 (0.28-2.13), 0.77 (0.26-2.25) and 0.38 (0.12-1.18), respectively (trend: $P = 0.032$). The corresponding odds ratios for males were 0.85 (0.45-1.55), 0.85 (0.45-1.56) and 0.57 (0.31-1.06) (trend: $P = 0.053$). (b) The risk reduction by Okinawan tea consumption was detected mainly in squamous cell carcinoma. Daily tea consumption significantly decreased the risk of squamous cell carcinoma in males and females, the odds ratios being 0.50 (95% confidence interval 0.27-0.93) and 0.08 (0.01-0.68), respectively. These findings suggest a protective effect of tea consumption against lung cancer in humans.

98. Olsen J, Kronborg O. Coffee, tobacco and alcohol as risk factors for cancer and adenoma of the large intestine. *Int J Epidemiol.* 1993 Jun;22(3):398-402.

Institute of Epidemiology and Social Medicine, University of Aarhus, Denmark.

Our aim was to estimate the association between smoking history, alcohol and tobacco smoking

and tumours of the large intestine. Associations were studied at an early stage of colorectal cancer in order to avoid bias in the information. In order to estimate the link between adenoma and cancer the exposures were analysed separately for cancer and adenoma patients. The study was conducted as a case-control study within a randomized trial for colorectal cancer among males and females aged 45-74 years. Cases initially included all individuals with a positive Haemoccult-II test in three screens and an age- and sex-matched reference group was selected from the test negatives. Subsequent colonoscopy defined the final case group, which consisted of 49 colorectal cancer patients, 171 with adenoma and 177 test positives with no diagnosis or with non-adenomatous polyps or haemorrhoids. Controls were 362 age- and sex-matched test negatives. Data were collected by blind telephone interviewing before the first clinical examinations of test positives. Smoking history, coffee or alcohol intake were not statistically significantly associated with colorectal cancer. For adenomas, the odds ratios (OR) were between 2.0 and 2.7 in all smoking categories. For smokers with > 40 years duration OR = 2.7 (95% confidence interval (CI): 1.6-4.7). Coffee consumption showed a clear protective effect. Consumers of 4-7 cups per day had an OR of 0.5 (95% CI: 0.3-0.8) and heavy consumers of > or = 8 cups had an OR of 0.3 (95% CI: 0.1-0.6). Neither tea nor alcohol consumption was related to adenoma risks.(ABSTRACT TRUNCATED AT 250 WORDS)

99. Ren A, Han X. Dietary factors and esophageal cancer: a case-control study. *Zhonghua Liu Xing Bing Xue Za Zhi*. 1991 Aug;12(4):200-4. [Article in Chinese]

A hospital-based case-control study of 112 patients with esophageal cancer was conducted to explore the association of dietary factors with cancer of the esophagus. Each case was matched to one non-cancerous patient from surgical department in the hospital of the same sex, age (+/- 5 years), occupation (farmer or nonfarmer), and residence as control. Multivariate conditional logistic regression analysis showed that the consumption of moldy grains (odds ratio (OR), 4.08), pickled vegetables (OR, 2.57), tea drinking habit (OR, 5.65), and hot food consumption (OR, 2.53) were significant risk factors for esophageal cancer. Intake of eggs (OR, 0.30) and higher proportion of flour and rice in the grain ration (greater than 30% vs. less than or equal to 30%) (OR, 0.43) were protective factors. Relations between factors were also discussed in the paper.

100. Risch HA, Burch JD, Miller AB, Hill GB, Steele R, Howe GR. Dietary factors and the incidence of cancer of the urinary bladder. *Am J Epidemiol*. 1988 Jun;127(6):1179-91. Department of Preventive Medicine and Biostatistics, University of Toronto, Ontario.

A case-control study of diet and bladder cancer was conducted during 1979-1982 in Edmonton, Calgary, Toronto, and Kingston, Canada. A total of 826 histologically verified cancer cases were individually matched by age, sex, and area of residence to 792 randomly selected population controls. Subjects were interviewed concerning their histories of exposure to a number of dietary factors, including table-top artificial sweeteners, low calorie foods and drinks, beverages containing caffeine or ethanol, and certain other food items. Also, subjects provided information on their past medical, occupational, and residential histories, in addition to their exposures to tobacco and other life-style factors. For the analysis, conditional logistic regression methods were used. Under adjustment for cumulative lifetime amount of cigarette smoking, the dietary

factors, with little exception, were not associated with significant alteration of risk for bladder cancer. In particular, ever regular use of artificial sweeteners did not appear to be associated with increased risk, either among men (odds ratio = 0.95, $p = 0.70$) or among women (odds ratio = 1.15, $p = 0.53$). However, daily intake of cholesterol, calculated from reported frequencies of consumption of nine relevant food items, suggested a mild increase in risk; the odds ratio estimate of trend was 1.07/100 mg average daily intake (i.e., $1.07(5.5) = 1.45$ for 550 mg cholesterol per day, as might be consumed in one egg; $p = 0.009$). A history of diabetes mellitus of onset after age 20 years also seemed to be associated with increased risk of bladder cancer (odds ratio = 1.65, $p = 0.019$), but this increase did not appear to be the result of use of insulin or other medications, or use of artificial sweeteners or low calorie foods. Thus, this study tends to confirm reports of a lack of association between use of artificial sweeteners and subsequent risk of bladder cancer.

101. Rosenberg L, Miller DR, Helmrich SP, Kaufman DW, Schottenfeld D, Stolley PD, Shapiro S. Breast cancer and the consumption of coffee. *Am J Epidemiol.* 1985 Sep;122(3):391-9.

The hypothesis has been raised that coffee consumption may increase the incidence of breast cancer, based on the report that fibrocystic breast disease, a risk factor for breast cancer, regresses after abstention from coffee and other methylxanthines. The relation between recent coffee consumption and the risk of breast cancer was evaluated in a case-control study, based on interviews conducted 1975-1982 at several mainly eastern US teaching and community hospitals. The responses of 2,651 women with newly diagnosed breast cancer were compared with those of 1,501 controls with nonmalignant conditions and 385 controls with cancers at other sites. The relative risk estimates for levels of coffee drinking up to seven or more cups daily, relative to none, approximated 1.0 with narrow 95% confidence intervals. After allowance for confounding, the relative risk estimate for drinking at least five cups a day was 1.2 (95% confidence interval, 0.9-1.6) using the noncancer controls and 1.1 (0.7-1.6) using the cancer controls. Coffee consumption was not associated with an increase in the risk of breast cancer among women with a history of fibrocystic breast disease, nor were tea or decaffeinated coffee associated with an increase in the risk of breast cancer. The results suggest that the recent consumption of coffee does not influence the incidence of breast cancer.

102. Rosenblatt KA, Thomas DB, Jimenez LM, Fish B, McTiernan A, Stalsberg H, Stemhagen A, Thompson WD, Curnen MG, Satariano W, Austin DF, Greenberg RS, Key C, Kolonel LN, West DW. The relationship between diet and breast cancer in men (United States). *Cancer Causes Control.* 1999 Apr;10(2):107-13.

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OBJECTIVES: The purpose of this paper was to investigate the relationship between food and beverage consumption and the development of breast cancer in men. **METHODS:** Possible relationships of dietary factors to risk of breast cancer in men were assessed in a case-control study conducted between 1983 and 1986. Cases ($N = 220$) were ascertained from ten population-based cancer registries. Controls ($N = 291$) were selected by random-digit dialing ($< \text{age } 65$) and from Health Care Financing Administration Medicare beneficiary lists ($\geq \text{age } 65$).

RESULTS: No trends in risk were observed with increasing intakes of specific foods, except for an increase in risk with citrus fruits. No increase in risk with increasing amounts of specific fats, vitamins, or minerals or with amounts of protein, fiber, carbohydrate, starches, nitrites, or alcohol consumed was observed, except for an increase in risk with dietary vitamin C consumption. A decreasing trend in risk with dietary niacin and with coffee and an increasing trend in risk with tea consumption were observed. No associations were found with use of any dietary supplements, including vitamin C. **CONCLUSIONS:** The observed associations are not consistent with findings from studies of breast cancer in women and probably do not represent causal relationships. Dietary factors are unlikely to be strong determinants of breast cancer in men.

103. Schairer C, Brinton LA, Hoover RN. Methylxanthines and breast cancer. *Int J Cancer*. 1987 Oct 15;40(4):469-73.

We investigated the relationship between methylxanthine consumption and breast cancer using data from a case-control study which included 1,510 cases and 1,882 controls identified through a nation-wide breast cancer screening program. There was no evidence of a positive association between methylxanthine consumption and risk of breast cancer. In fact, there was some suggestion of a negative association, particularly in women diagnosed after age 50. In addition, there was no evidence of increased risk with past or recent methylxanthine consumption, or with the consumption of caffeine or specific beverages, most notably brewed or instant caffeinated coffee and tea.

104. Setiawan VW, Zhang ZF, Yu GP, Lu QY, Li YL, Lu ML, Wang MR, Guo CH, Yu SZ, Kurtz RC, Hsieh CC. Protective effect of green tea on the risks of chronic gastritis and stomach cancer. *Int J Cancer* 2001;92:600-4.

Department of Epidemiology, UCLA School of Public Health, and Jonsson Comprehensive Cancer Center, Los Angeles, CA 90095-1772, USA.

Despite the declining trend, stomach cancer remains the second most common cancer worldwide. We examined the role of green tea consumption on chronic gastritis and stomach cancer risks. A population-based case-control study was conducted in Yangzhong, China, with 133 stomach cancer cases, 166 chronic gastritis cases, and 433 healthy controls. Epidemiologic data were collected by standard questionnaire and odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models in SAS. Inverse association was observed between green tea drinking and chronic gastritis and stomach cancer risks. After adjusting for age, gender, education, body mass index, pack-years of smoking and alcohol drinking, ORs of green tea drinking were 0.52 (95% CI: 0.29-0.94) and 0.49 (95% CI: 0.31-0.77) for stomach cancer and chronic gastritis, respectively. In addition, dose-response relationships were observed with years of green tea drinking in both diseases. The results provide further support on the protective effect of green tea against stomach cancer. This is the first time that green tea drinking was found to be protective against chronic gastritis, which may be of importance when designing intervention strategies for stomach cancer and its pre-malignant lesions in the high-risk population.

105. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. *Int J Cancer*. 1994 Jul 1;58(1):46-9.

Department of Preventive Medicine, University of Southern California School of Medicine, Los Angeles.

Risk factors for pancreatic cancer were examined in a cohort study of 13,979 residents of a retirement community. After 9 years of follow-up, 65 incident cases of pancreatic cancer were identified. An increased risk of pancreatic cancer was associated with a history of diabetes and cholecystectomy. Higher intake of vegetables, fruits, dietary beta-carotene, and vitamin C were each associated with a reduced risk of pancreatic cancer, although none of these associations was statistically significant. Risk of pancreatic cancer decreased with increasing tea consumption but was unrelated to coffee consumption. No strong or consistent association was seen between either smoking or alcohol consumption and risk of pancreatic cancer, but a consistent and significant increase in risk followed cholecystectomy.

106. Shibata K, Moriyama M, Fukushima T, Kaetsu A, Miyazaki M, Une H. Green tea consumption and chronic atrophic gastritis: a cross-sectional study in a green tea production village. *J Epidemiol* 2000;10:310-6.

Department of Public Health, School of Medicine, Fukuoka University, Japan.

Chronic atrophic gastritis (CAG) is well known as a precancerous lesion of the stomach, and *Helicobacter pylori* (*H. pylori*) infection increases the risk of CAG. While recent studies have reported that green tea consumption decreases the risk of gastric cancer, there has been no study analyzing the relationship between green tea consumption and the both risks *H. pylori* infection and CAG. We conducted a cross-sectional study on 636 subjects living in a farming village in Japan to examine the relationship among green tea consumption, *H. pylori* infection, and CAG. Smoking, alcohol drinking, consumption of four beverages, including green tea, and of five foods were investigated as lifestyle factors that may affect *H. pylori* infection and CAG. The measurement of *H. pylori*-IgG antibodies was used to define *H. pylori* infection, and serum pepsinogens were used to define CAG. The unconditional logistic regression model was used for analyzing each odds ratio (OR). *H. pylori* infection was positively associated with the risk of CAG (OR = 3.73; 95% confidence interval [CI], 2.59-5.36). High green tea consumption (more than 10 cups per day) was negatively associated with the risk of CAG, even after adjustment for *H. pylori* infection and lifestyle factors associated with green tea consumption (OR = 0.63; 95% CI, 0.43-0.93). These results support the hypothesis that high green tea consumption prevents CAG.

107. Simon D, Yen S, Cole P. Coffee drinking and cancer of the lower urinary tract. *J Natl Cancer Inst*. 1975 Mar;54(3):587-91.

The relationship between coffee drinking and cancer of the lower urinary tract (LUT) was investigated by a case-control study of white women identified from hospitals in urban areas of Massachusetts and Rhode Island. Data on coffee drinking, tea drinking, use of coffee additives, and cigarette smoking were obtained by mail questionnaire. Information was available for 135 women with LUT cancer and 390 controls. For women who usually drank 1+ cups of coffee per day, the risk ratio of having LUT cancer was 2.1 (95 percent confidence limits, 1.1-4.3),

compared to a risk of 1 for women who drank less or not at all. However, no dose-response relationship was demonstrated between LUT cancer and usual daily coffee consumption or "cup-years" of coffee drinking. The association of coffee with disease was no different, whether decaffeinated, nondecaffeinated, regular, or instant coffee had been drunk, or whether the coffee was brewed strong or weak. Use of nondairy creamers, saccharin, or cyclamates was not associated with increased risk of disease. The risk of LUT cancer for cigarette smokers relative to nonsmokers was 1.6 (1.0-2.4). The attendant dose-response relationship was statistically significant. The absence of a dose-response relationship between coffee drinking and LUT cancer suggested that the association observed was noncasual.

108. Slattery ML, West DW, Robison LM. Fluid intake and bladder cancer in Utah. *Int J Cancer*. 1988 Jul 15;42(1):17-22.

A population-based, incident case-control study was conducted in Utah to assess the relationship between fluid intake and bladder cancer. Cancer cases ($n = 419$) were identified through the Utah Cancer Registry, and controls ($n = 889$) were obtained through random digit dialing and the Health Care Financing Administration. After adjustment for cigarette smoking, age, sex, history of diabetes, and history of bladder infections using multiple logistic regression analysis, total fluid intake was not found to be related to bladder cancer development. Specific fluids related to bladder cancer risk were milk intake ($OR = 0.64$) and caffeinated coffee intake ($OR = 1.60$). A linear trend for a dose-response protective effect was observed for milk, while coffee increased risk only when 40 or more cups were consumed per week. Alcohol increased risk only when consumed at high levels (over 3.64 ounces or 103 g per week) by people who never smoked cigarettes ($OR = 2.37$). Likewise, tea consumption in non-cigarette smokers increased bladder cancer risk ($OR = 2.25$). Results from this study suggest that types of fluids consumed may play a role in the development of bladder cancer. Furthermore, it is hypothesized that the dietary components of these beverages may be related to the development of bladder cancer.

109. Slattery ML, West DW. Smoking, alcohol, coffee, tea, caffeine, and theobromine: risk of prostate cancer in Utah (United States). *Cancer Causes Control*. 1993 Nov;4(6):559-63. Department of Family and Preventive Medicine, University of Utah School of Medicine, Salt Lake City 84132.

Data from a population-based study of newly diagnosed cases of prostate cancer ($n = 362$) and age-matched controls ($n = 685$) conducted in Utah (United States) between 1983 and 1986 were used to determine if cigarette smoking, alcohol, coffee, tea, caffeine, and theobromine were associated with prostate cancer risk. These factors were examined since their use differs in the Utah population, which is comprised predominantly of members of the Church of Jesus Christ of Latter-day Saints (LDS or Mormon), from most other populations. Pack-years of cigarettes smoked, alcohol intake, and consumption of alcohol, coffee, tea, and caffeine were not associated with prostate cancer risk. Compared with men with very low levels of theobromine intake, older men consuming 11 to 20 and over 20 mg of theobromine per day were at increased risk of prostate cancer (odds ratio [OR] for all tumors = 2.06, 95 percent confidence interval [CI] = 1.33-3.20, and OR = 1.47, CI = 0.99-2.19, respectively; OR for aggressive tumors = 1.90, CI = 0.90-3.97, and OR = 1.74, CI = 0.91-3.32, respectively). We present biological mechanisms for a

possible association between prostate cancer and theobromine. This finding needs further exploration in studies with a wider range of theobromine exposures and more men with aggressive tumors.

110. Stocks P. Cancer mortality in relation to national consumption of cigarettes, solid fuel, tea and coffee. *Br J Cancer*. 1970 Jun;24(2):215-25.

Tea is positively related with cancer mortality of the intestine except rectum in both sexes and with larynx, lung and breast in females. Negative associations are indicated with the stomach in both sexes and uterus and leukaemia in females.

111. Su LJ, Arab L. Tea consumption and the reduced risk of colon cancer -- results from a national prospective cohort study. *Public Health Nutr*. 2002 Jun;5(3):419-25.
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OBJECTIVE: This study examines the relationship between tea consumption and colon cancer risk in the US population. **DESIGN:** Data from the National Health and Nutrition Examination Surveys NHANES I Epidemiologic Follow-up study (NHEFS) were used to examine the hypothesis. Cox proportional hazard models were used to examine the hypothesis of a protective effect of frequent tea consumption on colon cancer occurrence. **SETTING:** Due to differences in the precision of the exposure data, we analysed two cohort periods based on the NHEFS. Cohort I was based on the survey conducted at the NHEFS baseline and Cohort II began at the first follow-up. **SUBJECTS:** After excluding non-incidence cases and cases lost to follow-ups, there were 2359 tea users and 6498 non-tea users at baseline and 7656 tea users and 4514 non-tea users at the first follow-up. **RESULTS:** After adjusting for confounders, the relative risks of colon cancer are 0.57 (95% confidence interval (CI) 0.42, 0.78) and 0.59 (95% 1.00) for subjects who consumed ≤ 1.5 cups and > 1.5 cups per day, respectively, compared with non-tea users in Cohort II. Although more women consumed tea and the mean intake was higher, the preventive effect of tea consumption on colon cancer was found predominantly in men. The relative risks of colon cancer are 0.41 (95% 0.66) for men who consumed ≤ 1.5 cups day⁻¹ and 0.30 (95% 0.98) for > 1.5 cups day⁻¹ of tea consumption (P-value for trend < 0.01). No significant results were found in Cohort I. **CONCLUSIONS:** This study suggests an inverse association between colon cancer risk and habitual tea consumption.

112. Tajima K, Tominaga S. Dietary habits and gastro-intestinal cancers: a comparative case-control study of stomach and large intestinal cancers in Nagoya, Japan. *Jpn J Cancer Res*. 1985 Aug;76(8):705-16.

In this study, the authors found that coffee, black tea and Japanese tea showed no significant level of relative risk for cancer of the stomach, colon and rectum.

113. Tavani A, Pregnolato A, La Vecchia C, Favero A, Franceschi S. Coffee consumption and the risk of breast cancer. *Eur J Cancer Prev.* 1998 Feb;7(1):77-82.
Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy.

On the basis of clinical observations that some women with fibrocystic breast disease experienced resolution of the disease on eliminating methylxanthines from their diet, it has been suggested that coffee intake might be related to breast carcinogenesis. The relationship between coffee (mostly espresso and mocha), decaffeinated coffee and tea intake and breast cancer risk was therefore considered, combining data from two case-control studies, conducted in Italy between 1983 and 1994. Cases were 5,984 women, below age 75, with histologically confirmed breast cancer, and controls were 5,504 women admitted to hospital for a wide spectrum of acute, non-neoplastic, non-hormone-related diseases. The odds ratios (ORs) were estimated from multiple logistic regression equations including terms for study/centre, age, education, body mass index, smoking status, total alcohol intake, age at menarche and menopause, parity and age at first birth, use of oral contraceptives, use of hormone replacement therapy, history of benign breast disease and family history of breast cancer. No relationship was observed between coffee intake and the risk of breast cancer. The multivariate ORs were 1.17 (1.03-1.33), 1.17 (1.04-1.33), 1.21 (1.06-1.37) and 0.96 (0.83-1.11) for women drinking < 2, 2, > 2 to < 4 and > or = 4 cups/day compared to non-drinkers. Decaffeinated coffee was consumed only by 6-7% of cases and controls and the corresponding OR was 0.84 (0.72-0.98). Tea consumption was also low and not associated with the risk of breast cancer (OR 0.94, 95% CI 0.85-1.03). No significant heterogeneity was found for coffee intake across strata of age at diagnosis, education, body mass index, smoking status, total alcohol intake, age at menarche and menopause, parity, age at first birth, ever use of oral contraceptives, hormone replacement therapy, history of benign breast disease and family history of breast cancer. Thus, this study, based on a large data set, allows us to exclude the hypothesis that coffee intake is related to breast cancer risk in this Italian population.

114. Tavani A, Pregnolato A, La Vecchia C, Negri E, Talamini R, Franceschi S. Coffee and tea intake and risk of cancers of the colon and rectum: a study of 3,530 cases and 7,057 controls. *Int J Cancer.* 1997 Oct 9;73(2):193-7.
Istituto di Ricerche Farmacologiche Mario Negri, Milan, Italy. tavani@irfmn.mnegri.it

The relationship between coffee, decaffeinated coffee and tea intake and risk of cancers of the colon and rectum was considered combining data from 2 case-control studies, one conducted between 1985 and 1991 in Northern Italy and the other between 1991 and 1996 in 6 Italian centers. Cases were patients below age 80, with histologically confirmed cancer of the colon (n = 2,166) or rectum (n = 1,364), and controls were 7,057 patients admitted to hospital for a wide spectrum of acute, non-neoplastic, non-digestive tract diseases. Compared with coffee non-drinkers, the risk of colon cancer was reduced in drinkers of 4 or more cups/day [multivariate odds ratios (ORs) 0.73; 95% confidence intervals 0.60-0.89], with a significant trend in risk with dose; no significant association emerged between coffee drinking and risk of rectal cancer (OR 1.00 for drinkers of 4 or more cups/day). Decaffeinated coffee was consumed in small amounts by about 4% of cases and controls and the OR was 0.92 for colon and 0.88 for rectal cancers. Tea consumption was generally limited to 1 cup/day or to occasional intake and did not substantially

modify the risk of colon and rectal cancers. No significant heterogeneity was found for the inverse relationship between coffee intake and colon cancer risk across strata of age at diagnosis, sex, smoking status, total alcohol and meat and vegetable intake, while the protection of coffee was stronger in people eating 3 or more meals/day. Thus, our results confirm that coffee intake has a quantifiable protective effect on colon cancer risk.

115. Tewes FJ, Koo LC, Meisgen TJ, Rylander R. Lung cancer risk and mutagenicity of tea. *Environ Res* 1990 Jun;52(1):23-33.

To study the possible association between drinking tea and lung cancer, epidemiological and experimental materials were collected from the Chinese population in Hong Kong. In a retrospective study of 200 female lung cancer patients and 200 matched controls, all subjects were interviewed concerning their eating habits, smoking histories, and lifetime exposures to environmental pollutants. Analysis of the data demonstrated an adjusted and statistically significant increased lung cancer risk of 2.7 among those (23 patients) who drank green tea. Several brands of tea commonly drunk in Hong Kong were assayed for mutagenicity using Ames' assay. Significantly elevated levels of mutagenic activity were found to be present after metabolic activation using cell-free extracts of cecal bacteria from rats. These data suggest that further research is needed to understand the possible consequences to human health of ingestants taken at low doses but long duration over the normal lifespan, and the possible interactive effect between mutagens in tea and other ingestants and inhalants in human cancer etiology.

116. Trichopoulos D, Ouranos G, Day NE, Tzonou A, Manousos O, Papadimitriou C, Trichopoulos A. Diet and cancer of the stomach: a case-control study in Greece. *Int J Cancer*. 1985 Sep 15;36(3):291-7.

A case-control study focusing on the role of diet in the etiology of gastric cancer was undertaken in Piraeus, the sister city of Athens, in a population characterized by ethnic homogeneity but substantial heterogeneity with respect to dietary habits. The case series consisted of 110 consecutive patients with histologically confirmed adenocarcinoma of the stomach, admitted to two teaching hospitals during a 3-year period; the control series consisted of orthopedic patients admitted to a nearby hospital for accidents, fractures and other orthopedic disorders, during the same time period. Dietary histories concerning the frequency of consumption (per month or per week) of about 80 food items were obtained by the same interviewer. Cases reported significantly less frequent consumption of lemons, oranges, brown bread, and raw, salad-type vegetables (particularly lettuce, onions and cucumbers) and, independently, significantly more frequent consumption of pasta, beans and nuts. A relative risk of about 40 was found between extreme quintiles when the above 9 food items were combined in a linear risk score. Use of an index constructed from the study material will clearly overestimate the level of risk between the extreme quintiles, but nevertheless the risk differences appear noteworthy, and consistent with the international variation in the incidence of gastric cancer. No significant associations were found with alcoholic beverages, coffee or tea.

117. Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. Green tea and the risk of gastric cancer in Japan. *N Engl J Med* 2001;344(9):632-6.

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BACKGROUND: Although laboratory experiments and case-control studies have suggested that the consumption of green tea provides protection against gastric cancer, few prospective studies have been performed. **METHODS:** In January 1984, a total of 26,311 residents in three municipalities of Miyagi Prefecture, in northern Japan (11,902 men and 14,409 women 40 years of age or older), completed a self-administered questionnaire that included questions about the frequency of consumption of green tea. During 199,748 person-years of follow-up, through December 1992, we identified 419 cases of gastric cancer (in 296 men and 123 women). We used Cox regression to estimate the relative risk of gastric cancer according to the consumption of green tea. **RESULTS:** Green-tea consumption was not associated with the risk of gastric cancer. After adjustment for sex, age, presence or absence of a history of peptic ulcer smoking status, alcohol consumption, other dietary elements, and type of health insurance, the relative risks associated with drinking one or two, three or four, and five or more cups of green tea per day, as compared with less than one cup per day, were 1.1 (95 percent confidence interval, 0.8 to 1.6), 1.0 (95 percent confidence interval, 0.7 to 1.4), and 1.2 (95 percent confidence interval, 0.9 to 1.6), respectively (P for trend=0.13). The results were similar after the 117 cases of gastric cancer that were diagnosed in the first three years of follow-up had been excluded, with respective relative risks of 1.2 (95 percent confidence interval, 0.8 to 1.8) 1.0 (95 percent confidence interval, 0.7 to 1.5), and 1.4 (95 percent confidence interval, 1.0 to 1.9) (P for trend=0.07). **CONCLUSIONS:** In a population-based, prospective cohort study in Japan, we found no association between green-tea consumption and the risk of gastric cancer. (Comments NEJM and others).

118. Victora CG, Munoz N, Day NE, Barcelos LB, Peccin DA, Braga NM. Hot beverages and oesophageal cancer in southern Brazil: a case-control study. *Int J Cancer*. 1987 Jun 15;39(6):710-6.

There is a cluster of high-incidence areas of oesophageal cancer in south-eastern South America, including Southern Brazil, Uruguay and parts of Argentina. The present case-control study investigated the hypothesis that this may be due to the drinking of mate, a traditional beverage drunk at a very high temperature, and also studied the role of other known risk factors such as alcohol and tobacco. Cases (171) and age- and sex-matched controls (342) were recruited from hospitals in the State of Rio Grande do Sul in Southern Brazil. The crude odds ratio for daily mate drinkers was 1.92 relative to those drinking less frequently than daily ($p = 0.006$). Other risk factors included the drinking of cachaca (a sugar cane spirit), smoking, rural residence, low fruit consumption and high intake of meats. After adjustment for these variables through conditional logistic regression, the odds ratio associated with daily mate drinking was reduced to 1.47 (90% CI = 0.87-2.50). Although the study failed to provide evidence of a strong association between mate and oesophageal cancer, the cluster of high rates could be explained by relative risks of the magnitude observed. This is due to the fact that approximately 70% of adult males

and 50% of females are daily drinkers. In addition, this study revealed that alcohol, tobacco smoking and rural residence are the main risk factors for oesophageal cancer in this population and the fruit consumption confers some degree of protection.

119. Wakai K, Ohno Y, Obata K, Aoki K. Prognostic significance of selected lifestyle factors in urinary bladder cancer. *Jpn J Cancer Res* 1993 Dec;84(12):1223-9.

To examine the prognostic significance of lifestyle factors in urinary bladder cancer, we conducted a follow-up study of 258 incident bladder cancer patients, who were originally recruited in a case-control study in metropolitan Nagoya. Information on individual survivals was obtained from the computer data-file of the tumor registry of the Nagoya Bladder Cancer Research Group. Univariate analyses revealed significant associations of 5-year survivorship with educational attainment, marital status, drinking habits and consumption of green tea in males, and age at first consultation, histological type and grade of tumor, stage and distant metastasis in both sexes. After adjustment for age, stage, histology (histological type and grade) and distant metastasis by means of a proportional hazards model, drinking of alcoholic beverages was significantly associated with the prognosis of bladder cancer in males. Its adjusted hazard ratio was 0.46 (95% confidence interval: 0.26-0.79), favoring patients who had taken alcoholic beverages. In detailed analysis, ex-drinkers and all levels of current drinkers demonstrated hazard ratios smaller than unity, although no clear dose-response relationship was detected. No prognostic significance was found for such lifestyle factors as smoking habit, uses of artificial sweeteners and hairdye, and consumption of coffee, black tea, matcha (powdered green tea) and cola.

120. Wang M, Guo C, Li M. A case-control study on the dietary risk factors of upper digestive tract cancer. *Zhonghua Liu Xing Bing Xue Za Zhi*. 1999 Apr;20(2):95-7.

OBJECTIVE: To understand the effect of dietary factors in Yangzhong, Jiangsu Province-a high prevalence area in China. **METHODS:** A case-control study on 209 cases of upper digestive tract cancer was conducted. There were 68 cases of esophageal cancer, 69 cases of cardiac cancer and 72 cases of other gastric cancers including 129 males and 80 females aged 35-79 under the study. **RESULTS:** It is revealed that intake of pickled vegetables increases the ORs of esophageal, cardiac and other gastric cancers (OR = 2.82, OR = 5.17, OR = 2.92, respectively). It is also concluded that the intake of leftovers can elevate the ORs of esophageal and cardiac gastric cancer (OR = 1.88 and OR = 1.90) and over consumption of salt also elevates the OR of cardiac cancer (OR = 1.87). However, drinking green tea may decrease the ORs of esophageal and other gastric cancers (OR = 0.20 and OR = 0.28) while fruits consumption may reduce the OR of esophageal cancers (OR = 0.51). **CONCLUSION:** Tumors from upper digestive tract have some relations with diet factors but the effects vary with the differences of tumor sites, dose of exposure and area, etc.

121. Watanabe Y, Tada M, Kawamoto K, Uozumi G, Kajiwara Y, Hayashi K, Yamaguchi K, Murakami K, Misaki F, Akasaka Y, et al. [A case-control study of cancer of the rectum and colon] *Nippon Shokakibyo Gakkai Zasshi*. 1984 Feb;81(2):185-93. [Article in Japanese]

In order to elucidate risk factors of cancer of the rectum and the colon, a case-control study by a questionnaire was conducted on 65 pairs of cancer of the rectum and their controls and 138 of cancer of the colon and their controls. There was no definite relation between the past histories and cancer of the rectum and the colon. And also no definite relation was recognized between the blood types and cancer of the rectum and the colon. It is suggested that family history of gastric cancer was an increased risk factor for cancer of the rectum. It is suggested that eating beans and curds and drinking black tea were low risk factor for cancer of the rectum. **Drinking green tea might be associated with an increase in colorectal cancers as suggested by the data included in Table 9 and Table 10 although the difference between cases and controls was not significant.** Smoking seemed to be a low risk factor for cancer of the colon. However, it is dangerous to interpret that smoking lessens the risk of getting cancer of the colon, because controls mainly consisted of patients with peptic ulcer and other digestive diseases, among whom the proportion of smokers was considered to be high.

122. Whittemore AS, Paffenbarger RS Jr, Anderson K, Halpern J. Early precursors of pancreatic cancer in college men. *J Chronic Dis*. 1983;36(3):251-6.

From college data on 50,000 male former students, the records of 126 men who died of pancreatic cancer in a 16-50 yr follow-up period were compared with those of 504 surviving classmates with respect to physical and social characteristics. Return mail questionnaires received from 30,000 surviving alumni in 1962 or 1966 also were reviewed for characteristics that might predict altered risk of pancreatic cancer. Strong positive associations were found for cigarette smoking as reported both during college (p less than 0.001) and at time of questionnaire return ($p = 0.03$). Smoking 10 or more cigarettes per day during college corresponded to a relative risk of 2.6 with 95% confidence limits 1.5 to 4.6, and a positive smoking history at questionnaire return yielded a relative risk of 2.4 (1.1-5.1). No association was found for collegiate coffee drinking, either before or after adjustment for cigarette smoking. The relative risk for coffee drinking adjusted for smoking was 1.1 (0.7-1.8). In contrast, collegiate tea consumption was associated with a reduction in pancreatic cancer risk. The relative risk for tea drinking adjusted for smoking was 0.5 (0.3-0.9). Men who at college physical examination complained of occasional abdominal pain or discomfort had increased relative risk of pancreatic cancer (3.1 : 1.1-9.0) in the follow-up period.

123. Wu AH, Yu MC, Tseng CC, Hankin J, Pike MC. Green tea and risk of breast cancer in Asian Americans. *Int J Cancer*. 2003;106(4):574-9.
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There is substantial in vitro and in vivo evidence implicating tea polyphenols as chemopreventive agents against various cancers. However, epidemiologic data obtained from

mainly Western populations are not supportive of a protective role of tea, mainly black tea, in the etiology of breast cancer. Much less is known about the relationship between green tea and breast cancer risk. During 1995-1998, we conducted a population-based, case-control study of breast cancer among Chinese, Japanese and Filipino women in Los Angeles County and successfully interviewed 501 breast cancer patients and 594 control subjects. Detailed information on menstrual and reproductive factors; dietary habits, including intake of black and green tea; and other lifestyle factors was collected. Risk of breast cancer was not related to black tea consumption. In contrast, green tea drinkers showed a significantly reduced risk of breast cancer, and this was maintained after adjusting for age, specific Asian ethnicity, birthplace, age at menarche, parity, menopausal status, use of menopausal hormones, body size and intake of total calories and black tea. Compared to women who did not drink green tea regularly (i.e., less than once a month), there was a significant trend of decreasing risk with increasing amount of green tea intake, adjusted odds ratios being 1.00, 0.71 (95% confidence interval [CI] 0.51-0.99) and 0.53 (95% CI 0.35-0.78), respectively, in association with no, 0-85.7 and >85.7 ml of green tea per day. The significant inverse association between risk of breast cancer and green tea intake remained after further adjustment for other potential confounders, including smoking; alcohol, coffee and black tea intake; family history of breast cancer; physical activity; and intake of soy and dark green vegetables. While both green tea and soy intake had significant, independent protective effects on breast cancer risk, the benefit of green tea was primarily observed among subjects who were low soy consumers. Similarly, the protective effect of soy was primarily observed among subjects who were nondrinkers of green tea. In summary, our results point to an important role of both green tea and soy intake in relation to breast cancer risk in Asian-American women.

124. Yang CS, Chung JY, Yang GY, Li C, Meng X, Lee MJ. Mechanisms of inhibition of carcinogenesis by tea. *Biofactors*. 2000;13(1-4):73-9.

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Tea (*Camellia sinensis*) preparations have been shown to inhibit tumorigenesis at the initiation, promotion, and progression stages in different animal models. The anti-proliferative effects of tea polyphenols may be a key mechanism, especially in the NNK-induced lung tumorigenesis model with mice. Studies with cell lines have demonstrated that tea polyphenols inhibit cell proliferation and induce apoptosis. The effective concentrations used in these studies (20-100 microM) are usually higher than those observed in blood and tissues of humans and animals, which are in the low micromolar range. Glucuronide and sulfate conjugated and methylated catechins as well as ring fission products (due to intestinal microflora) have been observed in human plasma and urine. Purified green and black tea polyphenols inhibited the H-ras induced mitogen-activated protein kinases, AP-1 activities, and the growth of 30.7b Ras 12 and BES21 cells. Among the catechins, both the galloyl structure on the B ring and the gallate moiety are important for the inhibition. Both (-)-epigallocatechin-3-gallate and theaflavin-3,3'-digallate inhibited the phosphorylation of c-jun and p44/42 (ERK 1/2). More mechanistic and human studies in these areas will help us to understand the possible inhibitory action of tea against carcinogenesis in humans.

125. Ye WM, Yi YN, Luo RX, Zhou TS, Lin RT, Chen GD. Diet and gastric cancer: a case-control study in Fujian Province, China. *World J Gastroenterol*. 1998 Dec;4(6):516-518.

AIM:To explore the relationship between consumption of fish sauce, other dietary factors, living habits and the risk of gastric cancer. **METHODS:**From May 1994 to July 1995, a population-based 1:2 case-control study was carried out in high-risk areas of gastric cancer, Chang and Fuzhou cities, Fujian Province. Totally 272 cases and 544 age, gender-matched controls were included. Risk state analyses were made by SAS package. **RESULTS:**Risk state single-factor analysis indicated that gastric cancer risk rose with high intake of fish sauce (OR = 2.57), salted vegetables (OR = 1.41), salted/fried fish and small shrimps (OR = 1.57), low consumption of fresh vegetables (OR = 1.95), fresh citrus fruits (OR = 1.41), other fresh fruits (OR = 1.31), green tea (OR = 1.72), exposure to moldy foods (OR = 2.32), irregular dinners (OR = 5.47) and familial history of malignancy (OR = 3.27). No significant relationship was observed between smoking, drinking, salt intake, use of refrigerator and gastric cancer risk. The results of risk state conditional Logistic regression showed that fish sauce, salted/dried fish and small shrimps, irregular dinners, familial history of malignancy were included in the best risk set. The summary AOR for the four factors was 75.49%. **CONCLUSION:**High intake of fish sauce, salted foods, moldy foods, irregular dinners and familial history of malignancy were possible risk factors for gastric cancer, whereas fresh vegetables and fruits and green tea might have protective effects for gastric cancer.

126. Yu GP, Hsieh CC, Wang LY, Yu SZ, Li XL, Jin TH. Green-tea consumption and risk of stomach cancer: a population-based case-control study in Shanghai, China. *Cancer Causes Control*. 1995 Nov;6(6):532-8.

The effect of drinking Chinese green tea on the risk of stomach cancer was evaluated in a population-based case-control study conducted in Shanghai, China, from October 1991 to December 1993. Eligible cases were incident cases of primary stomach cancer diagnosed during the study period among residents of Hongkou district and Nanhui county aged under 80 years. Controls were selected from the same street or commune where the case resided and were matched to the cases on age (within three years) and gender. A total of 711 cases and 711 matched controls, more than 90 percent of the eligible subjects, completed the interview. Information was obtained on the types of tea used, age when habitual tea drinking started, frequency of new batches of tea leaves used per day, number of cups brewed from each batch, total duration of drinking for each batch, strength and temperature of the tea consumed. Statistical analysis was based on modelling through conditional logistic regression. After adjusting for age, gender, place of residence, education, birthplace, alcohol consumption, and cigarette smoking, the odds ratio (OR) comparing drinkers of green tea with nondrinkers was 0.71 (95 percent confidence interval = 0.54-0.93). The adjusted OR decreased with increasing number of new batches of the green tea consumed each day (P value trend = 0.006). With the largest series of stomach cancer cases to date, this study found green-tea consumption associated with lower risk of stomach cancer. Among drinkers of green tea, the risk of stomach cancer did not depend on the age when habitual green-tea drinking started. Green tea may disrupt gastric carcinogenesis at both the intermediate and the late stages.

127. Yu GP, Hsieh CC. Risk factors for stomach cancer: a population-based case-control study in Shanghai. *Cancer Causes Control*. 1991 May;2(3):169-74.

A population-based case-control study of stomach cancer was conducted among the teachers and staff of primary and middle schools in Shanghai. A total of 84 cases of stomach cancer were identified in all schools and 2,676 controls were drawn from the teachers and staff of a randomly selected sample of 40 primary and 15 middle schools. Data were analyzed by a multivariate logistic regression model. The analysis indicated that a positive family history of stomach cancer, cigarette smoking, low consumption of fruits, and low consumption of strong tea were significantly associated with stomach cancer incidence.

128. Yu MC, Mack TM, Hanisch R, Cicioni C, Henderson BE. Cigarette smoking, obesity, diuretic use, and coffee consumption as risk factors for renal cell carcinoma. *J Natl Cancer Inst*. 1986 Aug;77(2):351-6.

One hundred sixty incident cases of renal cell carcinoma under the age of 55 years and an equal number of age-(within 5 yr), race-, and sex-matched neighborhood controls were interviewed. Cigarette smoking was a risk factor for renal cell carcinoma in males [relative risk (RR) = 2.1, one-sided $P = .02$] but not in females (RR = 1.1, $P = .50$). Obesity was a significant risk factor in both males and females: The RR for a 4th quartile compared to a 1st quartile Quetelet's Index 10 years ago was 2.5 for males and 3.3 for females. Additional risk factors in females were diuretic use (RR = 4.5, $P = .002$) and daily coffee consumption (RR = 2.3, $P = .06$).

129. Yu Y, Hu J, Wang PP, Zou Y, Qi Y, Zhao P, Xe R. Risk factors for bladder cancer: a case-control study in northeast China. *Eur J Cancer Prev*. 1997 Aug;6(4):363-9.

Harbin Engineering University, China.

A case-control study of risk factors for bladder cancer was carried out in Heilongjiang Province, China. Between May 1989 and May 1990, 217 histologically confirmed cases of bladder cancer and 254 controls with non-neoplastic and non-urine system disease were recruited. Individuals were interviewed in the wards of six major hospitals. Controls were matched by sex, age and area of residence. Information was collected concerning economic status, occupation, histories of smoking and consumption of alcohol, use of tea, the taking of analgesics, dietary histories and previous diseases. Odds ratios (ORs) were calculated from stratified analysis and conditional logistic regression models. Increased risk was observed with increasing times per year and number of years of saccharine use. Compared with non-users, the use of saccharine for more than 19 times per year, and for more than 15 years, the adjusted ORs were 3.9 (95% CI = 1.8-8.67) and 5.1 (95% CI = 2.3-11.6), respectively. Statistically significant associations were also found for diseases related to the urinary system (OR = 2.8; 95% CI = 1.1-7.6). Increased consumption of fruit and vegetable may reduce the risk of bladder cancer. Cigarette smoking had no effect on the risk of bladder cancer in both genders. There was no association between the consumption of alcohol or tea, or types of water supply, with bladder cancer risk.

130. Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer*. 1993 Feb 20;53(4):601-7.

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A population-based, case-control study of pancreas cancer was undertaken in Opole, Poland, within the framework of the SEARCH Programme of the International Agency for Research on Cancer: this is the first aetiological study of pancreas cancer reported from Poland where the reported mortality rate has doubled since 1963. This study of pancreas cancer has provided some further supporting evidence of an association between increased pancreas risk with increasing levels of cigarette smoking. The risk rose with increasing lifetime cigarette consumption with a trend which was weakly significant ($p = 0.061$). Findings regarding lifetime tea and coffee consumption were not consistent with intake of either beverage increasing the risk of this disease. There was a strongly significant trend of decreasing risk with increasing lifetime consumption of tea ($p < 0.001$), which was also apparent when the analysis was restricted to subjects who were interviewed directly. For coffee consumption, which is low in Poland, there was also a negative association apparent in the data which was not statistically significant among the sub-set of subjects who were directly interviewed. The findings regarding alcoholic beverages were overall null, although the weakly positive trend in risk with spirits consumption ($p = 0.71$) may deserve further investigation in view of the special nature of the source of spirits (vodka) in Poland.

131. Zeegers MP, Dorant E, Goldbohm RA, van den Brandt PA. Are coffee, tea, and total fluid consumption associated with bladder cancer risk? Results from the Netherlands Cohort Study. *Cancer Causes Control*. 2001 Apr;12(3):231-8.

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OBJECTIVES: Coffee, tea, and fluid consumption have been thought to influence bladder cancer incidence. In a large prospective study, these associations were investigated. **METHODS:** In 1986, cohort members (55-69 years) completed a questionnaire on cancer risk factors. Follow-up was established by linkage to cancer registries until 1992. The multivariable case-cohort analysis was based on 569 bladder cancer cases and 3,123 subcohort members. **RESULTS:** The incidence rate ratios (RR) for men consuming <2 cups of coffee/day was 0.89 (95% CI 0.51-1.5) using the median consumption category (4- <5 cups/day) as reference. This RR increased to 1.3 (95% CI 0.94-1.9) for men consuming >7 cups/day, although no clear dose response association was found. The RRs decreased from 1.2 (95% CI 0.56-2.7) for women consuming <2 cups of coffee/day to 0.36 (95% CI 0.18-0.72) for women consuming >5 cups/day compared to the median consumption category (3- <4 cups/day). Men and women who abstained from drinking tea had a RR of 1.3 (95% CI 0.97-1.8) compared to those consuming 2- <3 cups of tea per day (median consumption category). The RR for men and women comparing highest to lowest quintile of total fluid consumption was 0.87 (95% CI 0.63 1.2). **CONCLUSION:** The data

suggest a possible positive association between coffee consumption and bladder cancer risk in men and a probable inverse association in women. Tea consumption was inversely associated with bladder cancer. Total fluid consumption did not appear to be associated with bladder cancer.

132. Zeegers MP, Tan FE, Goldbohm RA, van den Brandt PA. Are coffee and tea consumption associated with urinary tract cancer risk? A systematic review and meta-analysis. *Int J Epidemiol*. 2001 Apr;30(2):353-62.

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BACKGROUND: Narrative reviews have concluded that there is a small association between coffee consumption and an increased risk of urinary tract cancer, possibly due to confounding by smoking. No association for tea consumption has been indicated. This systematic review attempts to summarize and quantify these associations both unadjusted and adjusted for age, smoking and sex. **METHOD:** Thirty-four case-control and three follow-up studies were included in this systematic review. Summary odds ratios (OR) were calculated by meta-regression analyses. **RESULTS:** The unadjusted summary OR indicated a small increased risk of urinary tract cancer for current coffee consumers versus non-drinkers. The adjusted summary OR were: 1.26 (95% CI : 1.09-1.46) for studies with only men, 1.08 (95% CI : 0.79-1.46) for studies with only women and 1.18 (95% CI : 1.01-1.38) for studies with men and women combined. Neither unadjusted nor adjusted summary OR provided evidence for a positive association between tea consumption and urinary tract cancer. Even though studies differed in methodology, the results were rather consistent. We did not perform dose-response analyses for coffee and tea consumption due to sparse data. **CONCLUSIONS:** In accordance with earlier reviews, we found that coffee consumption increases the risk of urinary tract cancer by approximately 20%. The consumption of tea seems not to be related to an increased risk of urinary tract cancer.

133. Zhang M, Binns CW, Lee AH. Tea consumption and ovarian cancer risk: a case-control study in China. *Cancer Epidemiol Biomarkers Prev* 2002;11:713-8.
School of Public Health, Curtin University of Technology, Perth, WA 6845, Australia.

To investigate whether tea consumption has an etiological association with ovarian cancer, a case-control study was conducted in China during 1999-2000. The cases were 254 patients with histologically confirmed epithelial ovarian cancer. The 652 controls comprised 340 hospital visitors, 261 non-neoplasm hospital outpatients, and 51 women recruited from the community. Information on the frequency, type, and duration of tea consumption was collected by personal interview using a validated questionnaire. The risk of ovarian cancer for tea consumption was assessed using adjusted odds ratios based on multivariate logistic regression analysis, accounting for confounding demographic, lifestyle, and familial factors including hormonal status and family ovarian cancer. The ovarian cancer risk declined with increasing frequency and duration of overall tea consumption. The adjusted odds ratio was 0.39 for those drinking tea daily and 0.23 for those drinking tea for >30 years, compared with nontea drinkers. The dose response

relationships were significant, and the inverse association with ovarian cancer was observed for green tea consumption. The authors concluded that increasing frequency and duration of green tea drinking can reduce the risk of ovarian cancer.

134. Zheng W, Doyle TJ, Kushi LH, Sellers TA, Hong CP, Folsom AR. Tea consumption and cancer incidence in a prospective cohort study of postmenopausal women. *Am J Epidemiol*. 1996 Jul 15;144(2):175-82.

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Tea has consistently been shown to inhibit the occurrence of tumors in experimental animals. The evidence for such a beneficial effect in humans, however, is limited. The authors examined the association between non-herbal tea consumption and cancer incidence in a prospective cohort study of 35,369 postmenopausal Iowa women. In this cohort, information on the frequency of tea drinking and other dietary and lifestyle factors was collected by mailed survey in 1986. After 8 years of follow-up, 2,936 incident non-skin cancer cases were ascertained in this cohort through the State Health Registry of Iowa. Proportional hazards regressions were used to derive adjusted relative risks and 95% confidence intervals for the association between tea consumption and cancer incidence. After controlling for confounding factors, the authors found that regular tea consumption was related to a slight, but not statistically significant, reduced incidence of all cancers combined. Inverse associations with increasing frequency of tea drinking were seen for cancers of the digestive tract (p for trend, 0.04) and the urinary tract (p for trend, 0.02). For women who reported drinking ≥ 2 cups (474 ml) of tea per day, compared with those who never or occasionally drank tea, the relative risk for digestive tract cancers was 0.68 (95% confidence interval (CI) 0.47-0.98) and for urinary tract cancers, 0.40 (95% CI 0.16-0.98). Similar inverse associations were seen for specific digestive and urinary tract cancers, although site-specific analyses were not statistically significant. No appreciable association of tea drinking was found with melanoma, non-Hodgkin's lymphoma, or cancers of the pancreas, lung, breast, uterine corpus, or ovary. This study suggests that tea, one of the most popular beverages consumed worldwide, may protect against some cancers in postmenopausal women.

135. Zhong L, Goldberg MS, Gao YT, Hanley JA, Parent ME, Jin F. A population-based case-control study of lung cancer and green tea consumption among women living in Shanghai, China. *Epidemiology*. 2001 Nov;12(6):695-700.

Epidemiologic evidence regarding the association between the consumption of green tea and lung cancer is limited and inconclusive, although experimental studies have shown consistently that tea preparations and tea polyphenols may inhibit the induction of a variety of cancers, including lung cancer. In this population-based case-control study, we examined the association between past consumption of green tea and the risk of lung cancer. We identified 649 incident cases of primary lung cancer among women diagnosed from February 1992 through January 1994 using the population-based Shanghai Cancer Registry. We randomly selected a control group of 675 women from the Shanghai Residential Registry, frequency-matched to the expected

age distribution of the cases. Green tea consumption was ascertained through face-to-face interviews. We estimated adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) using unconditional logistic regression. Among nonsmoking women, consumption of green tea was associated with a reduced risk of lung cancer (OR = 0.65; 95% CI = 0.45-0.93), and the risks decreased with increasing consumption. We found little association, however, among women who smoked (OR = 0.94; 95% CI = 0.40-2.22). The inconsistency in the association between drinking tea and the risk of lung cancer reported in previous studies may in part be due to inadequate control of confounding of active smoking.

II. General comments by medical and scientific authorities on green tea as a chemopreventive beverage in cancer risk reduction with 49 references.

Forty-nine (49) articles expressing opinions on the relationship between green tea consumption and cancer risk in general. These are review articles, secondary reports based on data already published, observations or suggestions based on laboratory studies which may be related to application of green tea as a dietary supplement to reduce human cancer risk. A relevant short paragraph is extracted from the article under each title.

Practically, all the authors of these 49 articles are in favor of recommending green tea as a regular beverage with a potential chemopreventive effect to reduce the incidence of or to delay the occurrence of human cancers, namely to reduce cancer risk. However, a few raised the concern that epidemiological data have not been unanimously supportive of the benefits of tea drinking in reducing human cancers in large scale studies. Most investigators are beginning to recognize that the quality of green tea which determines the bioactivity of a cup of tea, the dose of green tea consumed in a study population, and the method of brewing the tea may greatly influence the outcomes of chemoprevention. An Internet search failed to uncover scientific articles objecting to drinking green tea as a potential chemopreventive agent unless a special contraindication exists.

These 49 references with abstract attached to each title are listed as follows.

1. Abdulla M, Gruber P. Role of diet modification in cancer prevention. *Biofactors*. 2000;12(1-4):45-51.

Carcinogenesis encompasses a prolonged accumulation of injuries at several different biological levels and include both genetic and biochemical changes in the cells. At each of these levels, there are several possibilities of intervention in order to prevent, slow down or even halt the gradual march of healthy cells towards malignancy. Diet modification is one such possibility. A number of natural foodstuffs, especially fruits and vegetables contain substantial quantities of molecules that have chemopreventive potential against cancer development. Such compounds include vitamins, trace elements and a variety of other molecules with antioxidant properties. Carotenoids, flavanoid polyphenols, isoflavones, catechins, and several other components that found in cruciferous vegetables are molecules that are known to protect against the deleterious effect of reactive oxygen species. A number of epidemiological and experimental studies have shown that vitamin C and E, Beta-carotene and the essential trace element selenium can reduce the risk of cancer. Consistent observations during the last few decades that cancer risk is reduced by a diet rich in vegetables, fruits, legumes, grains and green tea have encouraged research to identify several plant components especially phytochemicals that protect against DNA damage. Many of these substances block specific carcinogen pathways. Dietary supplements are part of an overall health program, along with a high intake of fruits and vegetables that help to combat damage to cells, which in turn may initiate cancer development. This paper will review current knowledge concerning diet modification and cancer prevention with special reference to minerals and trace elements.

2. Ahmad N, Mukhtar H. Green tea polyphenols and cancer: biologic mechanisms and practical implications. *Nutr Rev*. 1999 Mar;57(3):78-83.

Polyphenolic compounds in fruits and vegetables have been associated with lower risk of some diseases, including cancer. Recent research has shown that the polyphenolic antioxidants in green tea possess cancer chemopreventive effects. This review discusses the cancer chemopreventive effects associated

with green tea and the molecular mechanisms that underlie the broad anticarcinogenic effect of polyphenols in green tea.

3. Bartsch H. Studies on biomarkers in cancer etiology and prevention: a summary and challenge of 20 years of interdisciplinary research. *Mutat Res.* 2000 Apr;462(2-3):255-79.

Sensitive, specific methods have been developed that allow quantitative measurements of the metabolites of carcinogen metabolites and of DNA and protein adducts in humans exposed occupationally, environmentally and endogenously to genotoxic agents. The interrelationship between exposure to carcinogens, host risk factors and the responses of biomarkers has been examined in cross-sectional, ecological and case-control studies which provided new insights into the causes of cancer and the mechanisms of carcinogenesis. The identification of hitherto unknown DNA-reactive chemicals formed in the human body from dietary precursors and of carcinogenic components of complex mixtures has increased the possibility of establishing causal relationships in etiology. The identification of individuals and subgroups heavily exposed to carcinogens has led to the development of measures for avoiding or decreasing exposure to carcinogenic risk factors. New, ultrasensitive methods for measuring DNA adducts allow the quantification and structural elucidation of specific DNA damage in humans arising from oxidative stress and lipid peroxidation (LPO), which have been found to be the driving forces in several human malignancies. Background DNA damage in "unexposed" individuals has been shown unequivocally to be due to LPO products, and a significant interindividual variation in adduct levels has been shown in individuals with comparable exposure to carcinogens. Thus, pharmacogenetic variants with higher susceptibility to carcinogenic insults, due to genetic polymorphism in xenobiotic-metabolizing enzymes, have been characterized by a combination of genotyping and measurements of macromolecular adducts. Dosimetry has been used in human studies to evaluate the efficacy of interventions with chemopreventive agents like ascorbic acid, dietary phenols and green tea. Advances in the application of selected biomarkers in human studies are reviewed and illustrated by examples from the author's research conducted during the past two decades.

4. Bickers DR, Athar M. Novel approaches to chemoprevention of skin cancer. *J Dermatol* 2000;27:691-5.

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We demonstrated that green tea, black tea and constituent polyphenols protect against chemical- and ultraviolet B (UVB)-induced carcinogenesis and reduce the growth of established tumors in skin. We have also shown the efficacy of green and black tea extracts against UVB and psoralen + ultraviolet A (PUVA)-induced early damage in skin. Although PUVA is highly effective in treating certain skin diseases, careful follow-up studies of cohorts of patients have shown that similar to UVB, PUVA treatment increases the risk for cutaneous squamous cell carcinoma and melanoma. We have found that oral administration of a standardized green tea extract (SGTE) prior to and during treatment of SKH-1 mice diminished PUVA-induced skin hyperplasia and hyperkeratosis. SGTE-treatment also inhibited PUVA-induced accumulation of c-fos and p53 proteins and epithelial hyperproliferation. Both topical application and oral administration of SGTE after PUVA-treatment reduced skin inflammation and cell hyperproliferation. Topical application of SGTE to human skin prior to PUVA-treatment inhibited the delayed skin inflammatory response. Similarly, oral and topical administration of standardized black tea extract (SBTE) and its two major polyphenolic sub-fractions protect against UVB-induced erythema in SKH-1 mice. Furthermore, topical application of tea extracts to human volunteers protects against UVB-induced erythema. In summary, these studies indicate that tea extracts are effective in reducing UVB- and PUVA-mediated DNA damage, expression of early response genes and early inflammatory changes in